Expert Opinion

Effectiveness and safety of *Saccharomyces boulardii* for acute infectious diarrhea

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Introduction: Acute diarrhea continues to be a leading cause of morbidity, hospitalization and mortality worldwide and probiotics have been proposed as a complementary therapy in the treatment of acute diarrhea. Regarding the treatment of acute diarrhea, a few probiotics including *Saccharomyces boulardii* seem to be promising therapeutic agents.

Areas covered: We performed a systematic review and meta-analysis regarding the use of *S. boulardii* in the treatment of acute infectious diarrhea with relevant studies that searched with the PubMed, Embase, Scopus, Google Scholar, the Cochrane Controlled Trials Library, and the Cochrane Database of Systematic Reviews through October 2011. This review describes the effects of *S. boulardii* on the duration of diarrhea, the risk of diarrhea during the treatment (especially at the third day) and duration of hospitalization in patients with acute infectious diarrhea. This review also focused on the potential effects of *S. boulardii* for acute infectious diarrhea due to different etiological causes.

Expert opinion: *S. boulardii* significantly reduced the duration of diarrhea approximately 24 h and that of hospitalization approximately 20 h. *S. boulardii* shortened the initial phase of watery stools; mean number of stools started to decrease at day 2; moreover, a significant reduction was reported at days 3 and 4. This systematic review and meta-analysis of the efficacy of *S. boulardii* in the treatment of acute infectious diarrhea show that there is strong evidence that this probiotic has a clinically significant benefit, whatever the cause, including in developing countries. Therefore, with *S. boulardii,* the shortened duration of diarrhea and the reduction in hospital stay result in social and economic benefits.

Keywords: acute diarrhea, gastroenteritis, rotavirus, *Saccharomyces boulardii*

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1. Introduction

Diarrhea is defined as a change in bowel movements with an increase in the water content, volume and usually frequency of stools, mainly due to infectious causes. Despite improvements in public health and economic wealth, acute diarrhea continues to be a leading cause of morbidity, hospitalization and mortality worldwide [1]. More than one billion diarrhea episodes occur every year among children younger than 5 years of age, resulting in more than one million deaths, especially in developing countries [2]. Children living in resource-poor countries have more and more severe diarrheal episodes, as well as a higher risk of dehydration and death secondary to diarrhea. In these regions, diarrheal illness is caused by enteric bacteria and parasites, as well as viruses. Among children living in developed countries, diarrheal illnesses are usually caused by viruses and may result in hospitalization and increased

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Article highlights.

- Regarding the treatment of acute diarrhea probiotics seem to be promising therapeutic agents.
- *S. boulardii* can reduce the duration of diarrhea by approximately 1 day, shorten the initial phase of watery stools and decrease the length of hospital stay.
- *T*here is strong evidence that this probiotic has a clinically significant benefit in the treatment of acute infectious diarrhea in infants and children in developed and developing countries.
- *S. boulardii* is safe and well tolerated for administration to children with acute diarrhea.
- The shortened duration of diarrhea and the reduction in hospital stay result in a social and economic benefit.

This box summarizes key points contained in the article.

health-care costs [2,3]. Independent of socioeconomic status, virtually all children are infected before 3 – 5 years of age with rotavirus [2]. *Escherichia coli* strains are the most common cause of bacterial diarrhea worldwide and cause 30 – 40% of acute diarrheal episodes in children in developing countries [2,3]. Measures to prevent diarrhea include breast-feeding, hand washing, careful personal/general hygiene, clean food/water and vaccination for enteric diseases such as rotavirus, typhoid fever and cholera [4-7].

The main method of therapy for all individuals with dehydration caused by diarrhea is oral rehydration solution [1-8]. The objective is to avoid morbidity/mortality associated with dehydration. Water and electrolyte replacement does not substantially shorten the frequency/duration of diarrhea and has not been found to reduce stool volume, prompting a growing interest in adjunctive treatments [9]. Probiotics have been proposed as a complementary therapy in the treatment of acute diarrhea [9-11]. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [12]. The most widely evaluated outcomes are duration and severity of diarrhea and duration of hospitalization [10]. Regarding the treatment of acute diarrhea, a few agents, including *Lactobacillus GG, Saccharomyces boulardii and Lactobacillus reuteri,* seem to be promising therapeutic agents [10,11,13,14].

S. boulardii is a nonpathogenic yeast isolated from tropical fruit (lychee and mangosteens) in Indonesia [15]. Although closely related to *S. cerevisiae*, it has definitively different taxonomic, physiological, metabolic and genetic characteristics from other strains of *S. cerevisiae* [15-19]. Lyophilized *S. boulardii* are stable at room temperature, and the optimal growth temperature for *S. boulardii* is 37°C (i.e., human body temperature). *S. boulardii* survives passage through all levels of the digestive tract, is resistant to low pH and tolerant to bile acids. By contrast, other strains of *S. cerevisiae* prefer cooler temperatures and do not survive well in acid environments. *S. boulardii* is naturally resistant to antibiotics. *S. boulardii* is cleared from the stools 2–5 days after stopping administration [15-19].

The objective of the present report is to provide an update on the evidence [20] for the efficacy and safety of *S. boulardii* in the treatment of acute infectious diarrhea, based on the currently available peer-reviewed, randomized clinical trials.

2. Material & methods

We performed a systematic review of the literature regarding the use of *S. boulardii* in the treatment of acute infectious diarrhea. We also performed a meta-analysis on the available data according to the guidelines from The Cochrane Collaboration for the reporting the results of a meta-analysis. For the meta-analysis, only randomized controlled trials (RCTs) were included and preclinical studies, volunteer studies and uncontrolled studies were excluded. The following electronic databases were searched (unrestricted by language) through October 2011: PubMed, Embase, Scopus, Google Scholar, the Cochrane Controlled Trials Library and the Cochrane Database of Systematic Reviews. Additionally, secondary and manual searches of reference lists, other studies cross-indexed by authors, reviews, commentaries and conference abstracts were performed. The *ClinicalTrials.gov* Web site was also searched for RCTs that not yet published. We searched the databases using different combinations of the keywords '*Saccharomyces boulardii*,' 'boulardii,' 'probiotics,' 'yeast,' 'diarrhea,' 'gastroenteritis,' 'acute' and 'rotavirus.' We use a standardized approach that independently undertook the literature search, data extraction and quality assessment and we also assessed the risk of bias (adequacy of sequence generation, allocation concealment, blinding, presence of intention-to-treat analysis and comprehensive follow-up) in the studies that met the inclusion criteria. Regarding risk of bias, in all cases, an answer of 'yes' indicates a low risk of bias, and an answer of 'no' indicates a high risk of bias. Information on authors, publication year, study design, study location, methods, interventions, primary outcomes, adverse effects and results was extracted from each article. The primary objective of the meta-analysis was to determine the overall efficacy of *S. boulardii* in reducing the duration of acute infectious and reducing the percentage of children with diarrhea at various time intervals (especially at the third day of intervention) (**Table 1**). The secondary outcome measures evaluated included duration of hospitalization and mean number of stools at different time intervals. Exclusion criteria included the use of other strains of *S. cerevisiae* or other strains of probiotics; also excluded were preclinical studies, safety studies, case reports or case series, and duplicate reports. Titles and abstracts were screened in accordance with the above-described search strategy.

All potentially relevant articles were retained, and the full text version of these studies was examined to determine which studies satisfied the inclusion criteria. To be included in the meta-analysis, a study had to be an RCT comparing *S. boulardii* for the treatment of acute infectious diarrhea (with the use of placebo or active control or no treatment) [21,22].

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes.

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Cetina-Sauri *et al.* (1994)	Double-blind Placebo-controlled Trial Mexico	130 children 3 months to 3 years Acute watery diarrhea	*S. boulardii* 200 mg three times (n = 65) daily vs placebo (n = 65)	Efficacy, defined as fever than four stools in 24 h and absence of liquid stools	An initial aggressive reduction in the number of stools: from 7.5/day to 2.53 at the third day and a statistically significant difference from 24 h after the start of the fifth day in favor of *S. boulardii* ($p < 0.05$) The endpoint of cure of acute diarrhea was 85% in the *S. boulardii* group vs 40% in placebo ($p < 0.001$)
Castaneda Guillot *et al.* (1995)	Double-blind randomized Placebo-controlled Cuba	40 children 6 – 36 months	*S. boulardii* vs placebo for 1 month	Number of bowel movements Histomorphological findings	A decrease in the number of bowel movements was observed in the *S. boulardii* group (65 vs 15%) Combining clinical with histological criteria showed that 70% of the patients in the *S. boulardii* group showed a highly significant improvement, while only 10% in the placebo group did No adverse reactions due to *S. boulardii* were reported
Hafeez *et al.* (2002)	Randomized controlled trial Pakistan	101 children 6 – 60 months	ORS plus nutrition appropriate for age vs ORS + nutrition appropriate for age + *S. boulardii* (500 mg) for 6 days	Frequency of stools per day, consistency of stools and duration of illness	On day 2, the frequency of stools per day was 5.7 for the control group and 4.4 for the *S. boulardii* group ($p = 0.02$) 63% of patients had watery stools on day 3 in the *S. boulardii* group compared with 90% of controls The average duration of illness was 3.6 days *in S. boulardii* group compared with 4.5 days in controls
Mansour-Ghanaei *et al.* (2003)	Double-blind, randomized, controlled study Iran	54 adults Acute mucous bloody diarrhea due to amebiasis	Metronidazole 750 mg and iodoquinol 650 mg/day for 10 days or the same medication plus *S. boulardii* 250 mg orally	Follow-up at 2 and 4 weeks for duration of diarrhea, abdominal pain and microscopic evaluation of stools	Mean duration of diarrhea decreased by almost 25% and the duration of abdominal pain and fever decreased by almost 50% in the *S. boulardii* group Amebic cysts were not found in stool specimens of patients receiving *S. boulardii* compared with 18.5% of individuals in the control groups

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes (continued).

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Kurugöl *et al.* (2005)	Randomized, double-blind controlled study Turkey	200 children 3 months to 7 years old 41.5% rotavirus *Shigella flexneri* (n = 5), *Salmonella* (n = 4), amebiasis (n = 6), Giardia (n = 3), *Cryptosporidium* (n = 3)	*S. boulardii* 250 mg (n = 100) vs placebo (n = 100) for 5 days	The duration of diarrhea and the occurrence of side effects	The duration of diarrhea significantly decreased in children receiving *S. boulardii* compared with children receiving placebo (4.7 vs 5.5 days, p = 0.03) The number of stools showed a significant reduction in the *S. boulardii* group on days 2 and 3 Duration of hospital stay was shorter in *the S. boulardii* group (2.9 vs 3.9 days, p < 0.001) The frequency of watery diarrhea after the second day of treatment was significantly lower in the *S. boulardii* group
Billoo *et al.* (2006)	Randomized controlled study Pakistan	100 children 2 months to 12 years 16 – 20% rotavirus + 12 – 26% bacterial cause	*S. boulardii* (500 mg) plus WHO-CDD diarrhea protocol (n = 50) vs WHO-CDD diarrhea protocol (n = 50)	Number of stools, mean duration of diarrhea, follow-up for diarrhea	On days 3 and 6, there was a significant reduction in the reported number of stools in the *S. boulardii* group Mean duration of diarrhea was shorter in the *S. boulardii* group (3.5 vs 4.8 days, p = 0.001) *S. boulardii* also reduced the number of episodes of diarrhea by 50% in the subsequent 2 months
Besirbellioglu *et al.* (2006)	Double-blind placebo-controlled study Turkey	45 adults Giardiasis	Metronidazole plus *S. boulardii* vs metronidazole alone	At the end of second and fourth weeks with stool examinations	Median clearance of the symptoms was earlier in the *S. boulardii* plus metronidazole group (24 h) than in the metronidazole-alone group (30 h); however, the difference was not statistically significant At the end of the second week, *Giardia lamblia* cysts were not detected in the *S. boulardii* group but were detected in six cases (three symptomatic) in the metronidazole-alone group

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes (continued).

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Ozkan *et al.* (2007)	Prospective randomized placebo-controlled study Turkey	27 children 6 months to 10 years Acute diarrhea	*S. boulardii* vs placebo	Daily stool frequency Change in the immune response	Reduced daily stool frequency at day 3 and day 4 with *S. boulardii* therapy Significant increase in serum IgA The percentage of CD8 lymphocytes on day 7 was significantly higher in the *S. boulardii* group
Villarruel *et al.* (2007)	Randomized double-blind placebo-controlled study	88 children (72 children evaluated at first month) 3 – 24 months Acute diarrhea	*S. boulardii* 250 – 500 mg (n = 44) daily vs placebo (n = 44)	Number of stools, diarrhea lasting for > 7 days Duration of diarrhea and the effect when treatment was started within 48 h after the onset	The total number of stools and the number of watery stools passed on the fourth and seventh day were significantly lower in the *S. boulardii* group The total duration of diarrhea was significantly reduced in the *S. boulardii* group (4.7 vs 6.16 days; $p < 0.05$) A statistically significant decrease ($p < 0.05$) in the number of stools on the seventh day was seen in the *S. boulardii* group when treatment was started within 48 h of the onset of diarrhea
Canani *et al.* (2007)	Prospective single-blind randomized controlled trial Italy	600 children 3 – 36 months	ORT alone; LGG; *S. boulardii* (500 mg); *Bacillus clausii*; mix of *L delbrueckii var bulgaricus*, *Streptococcus thermophilus*, *L. acidophilus*, and *Bifidobacterium bifidum*; or *Streptococcus faecium* strain SF68	Primary outcomes were duration of diarrhea and daily number and consistency of stools. Secondary outcomes were duration of vomiting and fever and rate of admission to hospital	Total duration of diarrhea was similar between the *S. boulardii* and control groups
Vandenplas *et al.* (2007)	Double-blind prospective randomized controlled trial Indonesia India	188 children 3 – 33 months	93 *S. boulardii (500 mg)*; 95 placebo	Duration of diarrhea	The duration of diarrhea was 66.57 + 52.52 h in the control group versus 53.65 + 38.74 h (difference ~ 13 h or 20% of duration) in the *S. boulardii* group ($p < 0.05$) Significantly more children were cured in the *S. boulardii* group on day 3 (74% in placebo vs 86 % in the *S. boulardii* group ($p = 0.04$)

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes (continued).

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Htwe *et al.* (2008)	Myanmar Prospective, randomized controlled study Myanmar	100 children 3 months to 10 years (89%,3 months to 2 years) Acute watery diarrhea 21% *Escherichia coli*	*S. boulardii* (500 mg) plus ORS (n = 50) vs ORS (n = 50)	The duration of diarrhea and consistency and frequency of stools	The mean duration of diarrhea was shorter in the *S. boulardii* group (3.0 vs 4.7 days; $p < 0.05$) On day 3, *S. boulardii* group was two times more likely to experience reduction in the stool frequency (< 3 per day) On day 3, 76% of the *S. boulardii* group passed solid stools (vs 24% in controls) On day 4, the *S. boulardii* group was 13 times more likely to pass solid stools In Myanmar, acute watery diarrhea is mainly caused by EPEC, ETEC, *Salmonella*, *Shigella* and *Vibrio cholerae* *In E. coli* gastroenteritis (21%), stool consistency normalized more rapidly in the *S. boulardii* group
Dinleyici *et al.* (2009)	Prospective, randomized, open label study Turkey	50 children Acute bloody diarrhea due to amebiasis	Metronidazole (n = 25) vs metronidazole plus *S. boulardii* (n = 25)	Primary endpoints: duration of bloody diarrhea and microscopic detection of blood in the stools Secondary endpoints: duration of diarrhea, follow-up microscopic examination for amebiasis	The duration of bloody diarrhea was significantly shorter in the *S. boulardii* group (72 vs 42 h, $p < 0.001$) Cessation of diarrhea in the *S. boulardii* group occurred at 46 and at 74 h in metronidazole-alone group ($p = 0.001$) After 72 h of treatment, the frequency of bloody diarrhea (44 vs 11%) and diarrhea (76 vs 44%) were lower in the *S. boulardii* plus metronidazole group On day 5, 24% of children in metronidazole-alone group still had diarrhea and amebic cysts in the stool, whereas all patients in the *S. boulardii* group were negative for trophozoites and cysts

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes (continued).

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Savaş-Erdeve *et al.* (2009)	Open-prospective study Turkey	90 children 1 – 15 years *Entamoeba histolytica*-associated diS	Metronidazole vs metronidazole plus lyophilized *S. boulardii* for 10 days	Duration of acute diarrhea; daily record of frequency and consistency of stools and presence of bloody diarrhea; resolution time of vomiting, abdominal pain and fever during the treatment	The median durations of acute diarrhea and bloody diarrhea and the resolution time for symptoms including vomiting, fever and abdominal pain were not significantly different between groups There was no significant difference in the frequency of diarrhea recorded on daily sheets *S. boulardii* was well tolerated by all children, and no side effects were recorded
Eren *et al.* (2010)	Randomized prospective open-label clinical trial TURKEY	55 children 5 – 168 months Acute watery diarrhea 58% rotavirus	*S. boulardii* (250 – 500 mg) vs yoghurt fluid (a fluid extracted from yogurt made by a ferment containing *Lactobacillus bulgaricus* and *Streptococcus thermophilus*, 10^7 microorganism/ 100 ml, provided by manufacturer)	Comparison of clinical efficacy (duration of diarrhea, hospitalization and duration of vomiting)	Duration of diarrhea was shorter in the *S. boulardii* group (4.54 ± 2.36 vs 4.81 ± 1.79 days; not significant) On day 3, ITT analysis showed a statistically significant result favoring *S. boulardii* over yogurt fluid (16 patients (48.5%) versus 8 patients (25.5%); $p < 0.05$) On day 5, diarrhea had resolved in 70% of the *S. boulardii* group and 62% of the yogurt fluid group A significant reduction in daily stool frequency was observed on day 3 in rotavirus-infected patients in the *S. boulardii* group
Grandy *et al.* (2010)	Randomized double-blind controlled trial Bolivia	64 children 1 – 23 months Acute rotavirus diarrhea	ORT plus placebo, ORT plus *S. boulardii* (500 mg), ORT plus a compound containing *L. acidophilus*, *L. rhamnosus*, *Bifidobacterium longum* and *S. boulardii*	Duration of diarrhea, fever, vomiting and hospitalization	Total duration of diarrhea was significantly shorter in children receiving *S. boulardii* ($p = 0.04$) Duration of fever was significantly shorter in the group receiving *S. boulardii* ($p = 0.0042$)

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes (continued).

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Correa *et al.* (2011)	Double-blind randomized placebo-controlled trial Brazil	176 children 6 – 48 months Acute diarrhea 72 h before hospitalization 57.4% rotavirus positive	*S. boulardii* (n = 90) daily vs placebo (n = 86) for 5 days	Clinical cure of diarrhea (frequency < 3 times) or improvement in the stool consistency for at least 24 h	On day 3, the frequency of patients who remained with diarrhea was lower in the *S. boulardii* group (32.2 vs 59.2%; $p < 0.01$) ITT analysis showed that the frequency of patients with diarrhea on day 3 was lower in the *S. boulardii* group, with a statistically significant reduction in risk (RR = 0.54, 95% CI: 0.38 – 0.66) The beneficial effect of *S. boulardii* was observed especially in rotavirus cases (persistent diarrhea in 29.2 vs 64.4% of patients compared with 41.2 and 54.3% in patients with non-rotaviral diarrhea
Dalgic *et al.* 2011	Prospective, open, randomized controlled trial Turkey	480 children 1 – 28 months Acute rotavirus diarrhea	Eight different treatment groups, each including 60 children: *S. boulardii (250 mg),* zinc; lactose-free formula, *S. boulardii* + plus zinc; *S. boulardii* plus lactose-free formula; zinc plus lactose-free formula; *S. boulardii* plus zinc plus lactose-free formula; only oral and/or parenteral rehydration solutions	The duration of diarrhea Number of vomiting episodes, the number of bowel movements Safety and tolerability Number of hospitalization days	The duration of diarrhea was significantly reduced in the patients receiving zinc plus *S. boulardii* compared with the control group ($p < 0.05$) and the *S. boulardii* alone The shortest median duration of diarrhea was observed in children receiving zinc + *S. boulardii* (3.11 ± 1.81 days) The duration of hospitalization (4.1 days) was shorter in the zinc plus *S. boulardii* group than in the controls and the other groups including zinc alone and *S. boulardii* alone

Table 1. Descriptions of the published studies about *Saccharomyces boulardii* in acute diarrhea due to all infectious causes (continued).

Authors	Study description Country	Age groups condition	*S. boulardii* vs comparators	Endpoint	Results and notes
Riaz *et al.* 2011	Prospective, double-blind randomized controlled trial India	3 – 59 months Acute diarrhea (admitted less than 48 h of onset) 14/93 rotavirus positive	Placebo (n = 54) or *S. boulardii* (54) as 500 mg	The primary outcome variable was duration of diarrhea	The mean post-intervention duration of diarrhea was significantly shorter in the *S. boulardii* group (52.08 ± 24.57 vs 64.04 ± 30.43 h) The time of appearance of the first semi-formed stool in the *S. boulardii* group (39.48 ± 23.09 h) was significantly shorter than the placebo group (54.13 ± 28.21 h) The mean total ORS intake was significantly lower and mean time to first rehydration was significantly less in the *S. boulardii* group

We used the Cochrane Review Manager (RevMan, Version 5.1, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) for analysis. The weighted mean difference (WMD) between the treatment and control groups was selected to represent the difference in continuous outcomes. To perform a meta-analysis of continuous data using mean differences, one needs to extract the mean values of the outcomes, the standard deviations of the outcomes and the number of participants in whom the outcome was assessed in the *S. boulardii*-treated and control groups. The binary measure for individual studies and pooled statistics was reported as the risk ratio between the *S. boulardii* and control groups with 95% confidence intervals. To perform a meta-analysis of binary outcomes, one needs to extract the number of subjects with an event and the total number of subjects in the group. The weight given to each study was based on the inverse of the variance. Heterogeneity was quantified by χ^2 and I^2, which can be interpreted as the percentage of the total variation between studies that is attributable to heterogeneity rather than to chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Because there was substantial heterogeneity, all analyses were based on the random effects model if it was still considered appropriate to pool the data. Publication bias was evaluated with a test for asymmetry of the funnel plot.

3. Results

The literature search yielded 381 articles and 19 clinical trials [23-41] have been selected for *S. boulardii* use for acute infectious diarrhea. Seventeen of these studies were performed in children; one study was performed in adults with diarrhea due to *Entamoeba histolytica* [26] and another study was performed in adults with giardiasis [29] (see Supplement I). All were published in English. The daily dose of *S. boulardii* varied between 250 and 750 mg. All of these studies have been performed with same *S. boulardii* strain by the same company (Biocodex®, France). The studies evaluated in this report included ambulatory patients, hospitalized patients or both. For meta-analysis, only 13 studies have been selected. Six studies have been excluded because of performing in adults and/or reported in cases with giardiasis or amebiasis.

Most studies reporting successful treatment of infectious diarrhea by *S. boulardii* were performed in young children. The results are similar between the groups who had received different doses and dosing schedules of *S. boulardii*. Many of these patients suffered from rotavirus infections or had acute watery diarrhea due to both viral and bacterial infections. Studies about *S. boulardii* have been performed in both developed and developing countries, which have different serologic and epidemiological criteria for establishing the etiology of diarrhea and evaluating diarrhea-related risk factors. Withdrawals and dropouts

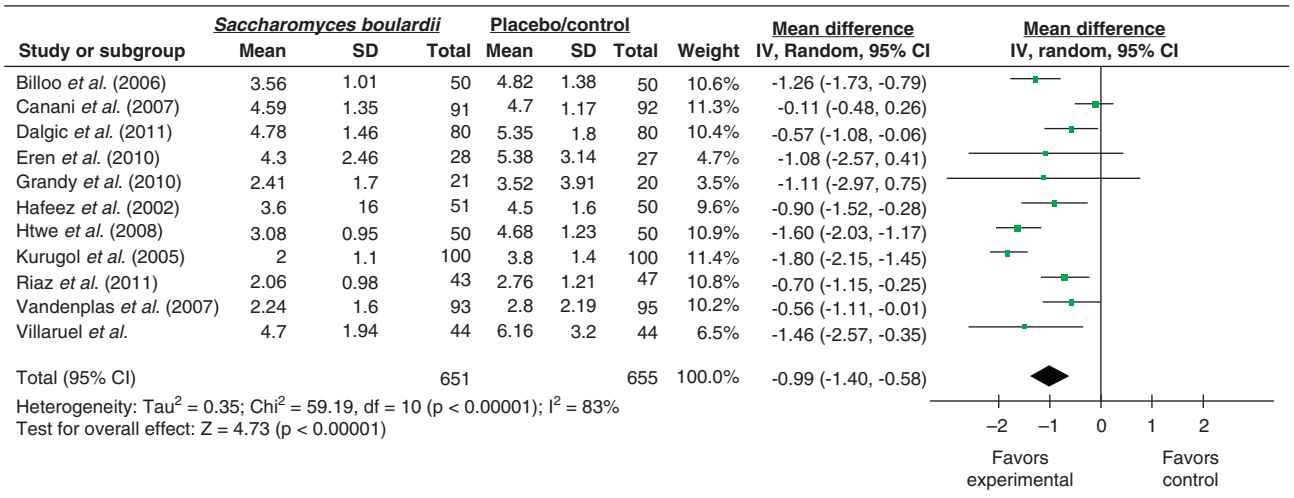

Figure 1. Duration of diarrhea (days): comparison between the *Saccharomyces boulardii*-treated and control groups.

were described adequately in all studies. All trials included an adequate number of participants in the final analysis.

Regarding the duration of diarrhea, this meta-analysis studied 11 RCTs with a total of 1306 patients (all children, 651 in the *S. boulardii* group and 655 controls). In this meta-analysis, we showed that *S. boulardii* significantly reduced the duration of acute infectious diarrhea compared with controls. The pooled WMD was –0.99 days (approximately 24 h, 95% CI: -1.40 to -0.58) with a fixed model and remained significant in a random-effect model for those treated with *S. boulardii* compared with placebo (**Figure 1**) [25,27,28,31-34,36,38,40,41].

Based on the results of nine RCTs involving 1128 children, *S. boulardii* significantly reduced the risk of diarrhea at the third day of illness (1128 children, RR: 0.52; 95% CI: 0.42 – 0.65, as shown in **Figure 2**) [23,25,27,31,33,34,37,39,41]. Other parameters are summarized in **Table 2**. Regarding the duration of hospitalization, we analyzed 449 children and showed that *S. boulardii* significantly reduced the duration of hospitalization due to acute infectious diarrhea compared with controls. The pooled WMD was -0.84 days (~ -20 h, 95% CI: -1.14 to -0.54) with a fixed model and remained significant in a random-effect model. The mean number of stools started to decrease at day 2 of the *S. boulardii* treatment (pooled WMD is -0.67 (-0.93, -0.41) among 188 patients); moreover, a significant reduction in the mean number of stools compared with controls was reported at day 3 and day 4 in the *S. boulardii* intervention group (WMD -1.61 (-1.83, -1.39) at day 3, -1.32 (-1.56, -1.09) at day 4). The incidence of diarrheal symptoms started to decrease at day 2 in the *S. boulardii* group (RR: 0.63 (0.54, 0.73)), and more than 50% of patients had no diarrhea at day 3 in the *S. boulardii* group (RR: 0.52 (0.42 – 0.65). Adverse effects associated with *S. boulardii* were not reported in any of these RCTs.

All included trials had a number of methodological limitations; however, more than 80% of these studies have follow-up and intention-to-treat analysis. Significant heterogeneity was found for the duration of diarrhea (I^2 = 83%) and risk of diarrhea at the third day of illness (I^2 = 63%). Publication bias was formally assessed using a funnel plot and showed asymmetry. Study limitations also included a sample size in some trials. However, funnel plot asymmetry might be due to publication bias, poor methodological quality or chance as well as true heterogeneity due to small sample size [22].

4. Discussion

In 2010, Allen *et al.* [42] published current Cochrane analysis about the probiotics for treating acute infectious diarrhea, and probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea. According to the recent meta-analysis by Szajewska *et al.* [43] that was based on the pooled results of six RCTs involving 756 children, *S. boulardii*, compared with placebo or no intervention, reduced the duration of diarrhea by 22 h (WMD -22, CI -26 to -18). Our meta-analysis studied 11 RCTs for a total of 1306 patients (all children, 651 on *S. boulardii* group and 655 controls) regarding the duration of diarrhea. *S. boulardii* significantly reduced the duration of acute infectious diarrhea compared with controls by ~ 24 h (-0.99 days 95% CI: -1.40 to -0.58). The duration of diarrhea has been reduced in children in *S. boulardii* groups and similar between different countries (in *S. boulardii* group, duration was 4.7 days in Kurugöl and Koturoğlu [27] study from Turkey and 4.7 days in Villarruel *et al.* [31] study from Argentina). Villarruel *et al.* [31] showed that children given *S. boulardii* within 48 h of the onset of diarrhea had significantly fewer stools than those given the product after more than 48 h of diarrhea. In Brazil, Correa *et al.* [39] showed a reduction in the duration of diarrhea when *S. boulardii* was given to children within 72 h after the onset of acute diarrhea. In India, Riaz *et al.* [41] performed a double-blinded, RCTs on 108 children aged between 3 and 59 months with acute-onset

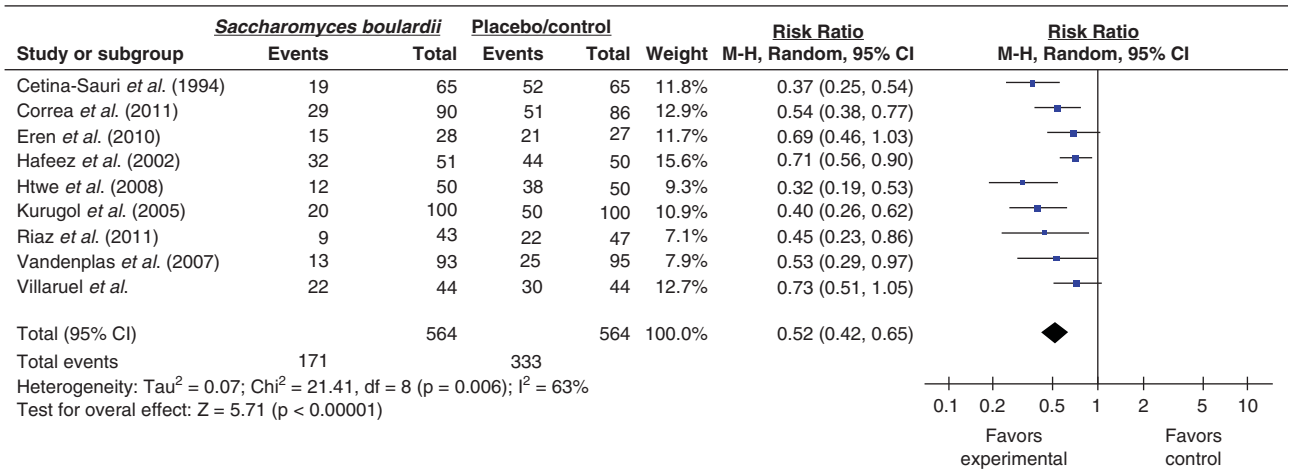

Figure 2. Comparison at the third day of diarrheal symptoms between *Saccharomyces boulardii* and controls.

diarrhea (of less than 48 h): the duration of diarrhea was significantly shorter in the *S. boulardii* group. Nine of eleven controlled clinical trials using *S. boulardii* showed it to be beneficial in children with acute infectious diarrhea. Two studies showed that *S. boulardii* had no effect on the duration of diarrhea in children. Canani *et al.* [32] conducted a multicenter randomized clinical trial to compare the efficacy of five probiotic preparations, including *S. boulardii,* in 571 children aged 3 – 36 months. There was no difference between *S. boulardii* and the control group. This study was not blinded; furthermore, the trial location and ambulatory nature of intervention may help to explain why *S. boulardii* had no effect in this study. Dalgic *et al.* [40] reported a prospective, randomized, single-blinded controlled trial in children with acute diarrhea due to rotavirus in Turkey. In patients receiving *S. boulardii* alone, there was no difference in the duration of nausea and vomiting or in the length of hospital stay compared with the control group. However, this study showed that the combination of probiotics and zinc decreased the duration of diarrhea and hospitalization compared with the control group. Despite the results of these two trials, there appears to be evidence that *S. boulardii* is effective in treating infectious diarrhea and that treatment with *S. boulardii* appears to reduce the duration of diarrhea by approximately 1 day.

The data from nine RCTs involving 1128 children showed that *S. boulardii* could significantly reduce the risk of diarrhea at the third day of diarrhea (RR: 0.52; 95% CI: 0.42 – 0.65) [23,25,27,31,33,34,37,39,41]. The mean number of stools began to decrease at day 2 of the *S. boulardii* treatment, and a significant reduction in the mean number of stools was achieved by day 3 and day 4 in patients receiving *S. boulardii* intervention compared with controls at day 3 and day 4. The presence of diarrhea started to decrease at day 2 in *S. boulardii*-treated patients and more than 50% of patients receiving *S. boulardii* had no diarrhea at day 3, a significantly lower rate that in the control group. According to Kurugöl and Koturoğlu's study [27], the number of stools was significantly lower in the *S. boulardii* group than in the placebo group after the second day of treatment. Htwe *et al.* [34] showed that stools had a normal consistency on day 3 in 76% of patients in the *S. boulardii* group. On day 4, patients were 13 times more likely to pass solid stools after receiving *S. boulardii* plus ORS than patients who received only ORS. Eren *et al.* [37] showed that diarrhea had resolved in significantly more children on day 3 in the *S. boulardii* group than the control group. A significant reduction in stool frequency was observed at day 1 with *S. boulardii* and the duration of diarrhea was shorter in the *S. boulardii* group, expressed as a significantly higher number of patients with normal stools on day 3. Riaz *et al.* [41] showed that the time of appearance of the first semi-formed stool in the *S. boulardii* group (39.4 ± 23.0 h) was significantly shorter than the placebo group (54.1 ± 28.2 h).

In terms of the duration of hospitalization, we analyzed 449 children and showed that, compared with controls, *S. boulardii* significantly reduced the duration of hospitalization due to acute infectious diarrhea approximately 20 h. Kurugöl and Koturoğlu [27] showed that *S. boulardii* treatment reduced hospitalization by 1 day in their RCT. However, Dalgic *et al.* [40] did not find any significant difference in the duration of hospitalization in patients receiving only *S. boulardii* compared with controls. Grandy *et al.* [38] also showed that the total length of hospital stay did not decrease with a 1-day decrease in diarrhea duration. This result was felt to be due to parents' requests, particularly among families who lived far away from the hospital, to keep the child in the hospital for another day of observation to prevent readmission.

S. boulardii treatment appears to improve other outcome measures as well. In their study, Kurugöl and Koturoğlu [27] showed that diarrhea persisted for more than 14 days in 4% of patients in the placebo group; however, only 1% of patients who were treated with *S. boulardii* had persistent diarrhea.

Table 2. Clinical effectiveness of *S. boulardii* versus control in patients with acute infectious diarrhea.

Outcomes from RCTs	Numbers (N)	Statistical method	Effect size
Duration of diarrhea (days)	1306	WMD	-0.99 (-1.39, -0.60)
Duration of hospitalization (days)	449	WMD	-0.84 (-1.14, -0.54)
Diarrhea on day 2	476	RR	0.63 (0.54, 0.73)
Diarrhea on day 3	1128	RR	0.52 (0.42 – 0.65)
Diarrhea on day 4	388	RR	0.30 (0.08, 1.17)
Diarrhea on day 5	618	RR	0.27 (0.16, 0.44)
Diarrhea on day 7	188	RR	0.39 (0.20, 0.75)
Mean number of stools reported on day 1	320	WMD	-0.57 (-1.27, 0.13)
Mean number of stools reported on day 2	188	WMD	-0.67 (-0.93, -0.41)
Mean number of stools reported on day 3	358	WMD	-1.61 (-1.83, -1.39)
Mean number of stools reported on day 4	245	WMD	-1.32 (-1.56, -1.09)
Mean number of stools reported on day 6	201	WMD	-0.83 (-2.52, 0.86)
Mean number of stools reported on day 7	88	WMD	-0.90 (-1.37, -0.43)

Negative values indicate that the outcome was shorter (or reduced) in the *S. boulardii* group compared with the controls.
RCTs: Randomized controlled trials; RR: Relative risk; WMD: Weighted mean difference.

Villarruel *et al.* [31] showed that diarrhea persisted for more than 7 days in 7% of patients treated with *S. boulardii*, compared with 27% of patients receiving placebo. Billoo's study [28] in Pakistan also showed that *S. boulardii* was effective in reducing the number of children with prolonged diarrhea. Recently, Riaz *et al.* [41] showed that mean total ORS intake was significantly lower and that mean time to first rehydration was significantly less in a group of patients treated with S. *boulardii*.

Studies have shown that *S. boulardii* treatment can have beneficial effects in acute diarrhea due to bacterial as well as viral causes. In Kurugöl and Koturoğlu's study [27] that demonstrated a 1-day reduction in the duration of diarrhea and a 1-day reduction in the length of hospital stay, 41.5% of the study population was rotavirus antigen positive, and 10% of cases were due to *Shigella flexneri*, *Salmonella typhimurium*, *Entamoeba histolytica, Giardia lamblia* or *Cryptosporidium*. Villarruel *et al.* [31] showed that the incidence of diarrhea was lower in patients with rotavirus (29.2%) than in the non-rotaviral group – (41.2%) 3 days after beginning treatment with *S. boulardii*. In Billoo *et al.*'s study [28] including 100 Pakistani children, rotavirus was detected only in 16 and 20% of the children in the treatment and control groups, respectively. Htwe *et al.* [34] showed that *S. boulardii* provided significant benefits in the duration of diarrhea in children in Myanmar, where acute diarrhea is caused mainly by enteropathogenic and enterotoxigenic *E. coli*. In the subgroup with *E. coli* gastroenteritis (21%), stool consistency also normalized more rapidly in the *S. boulardii* group. In Correa *et al.*'s study [39], an average of 57.4% of children had diarrhea with positive rotavirus test. The beneficial effects of probiotic treatment were observed mainly among patients presenting with rotaviral diarrhea. Recently, Riaz *et al.* [41] performed a double-blinded, RCT among 108 children, 15% of whom were rotavirus positive. Several controlled trials have shown that *Lactobacillus GG* has both therapeutic and prophylactic effects in children with viral, but not bacterial diarrhea [44]. However, results of RCTs performed on children with bacterial diarrhea suggest that *S. boulardii* seems efficacious and safe in children with acute bacterial diarrhea. However, further RCTs are needed to test the efficacy of *S. boulardii* specifically for the treatment of bacterial diarrhea.

In addition to treating viral and bacterial diarrhea, *S. boulardii* may also be able to treat diarrhea due to giardiasis and amebiasis. Castaneda Guillot *et al.* [24] suggest that *S. boulardii* may be effective in preventing the occurrence of new episodes of diarrhea in a 2-month long-term follow-up in patients with giardiasis and improved tolerance of feeding in children. Besirbellioglu *et al.* [29] randomized 65 Turkish adults with giardiasis to either *S. boulardii* or placebo for 10 days. Both groups also received metronidazole for the same duration. Two weeks later, both groups reported a resolution of their diarrhea; however, none of the patients treated with *S. boulardii* had detectable giardia cysts, while a significantly greater percentage of patients receiving placebo (17%) still carried giardia cysts. In Turkey, we performed a prospective, randomized, open clinical trial in 50 children with acute bloody diarrhea caused by *E. histolytica* to evaluate the efficacy of *S. boulardii* in addition to metronidazole for 7 days [35]. The addition of *S. boulardii* to metronidazole in amebiasis significantly decreased the duration of (bloody) diarrhea and enhanced clearance of cysts. In our study group, cessation of diarrhea in children that received the combination of *S. boulardii* and metronidazole was more rapid than that in children that received metronidazole alone [35]. Mansour-Ghanaei *et al.* [26] assessed the effects of adding *S. boulardii* to the standard treatment for invasive amebiasis in 57 adults in Pakistan. Adding *S. boulardii* to the usual treatment of acute amebic dysentery decreased the mean duration of diarrhea by almost 25%, decreased the duration of abdominal pain and fever by almost 50% and no amebic cysts were found in the *S. boulardii* group at week 4 while cysts were found in 18.5% of standard treatment group. Coadministration of lyophilized *S. boulardii* with conventional treatment for acute amebic colitis significantly decreased the duration of symptoms and chances of

being cyst carriers after 4 weeks. Contrary to these results, however, Savaş-Erdeve *et al.* [36] showed no effect of adding *S. boulardii* to antibiotic treatment for amebiasis-associated acute diarrhea in children. The median duration of acute diarrhea, the median number of stools and duration of bloody diarrhea, fever, abdominal pain and vomiting were similar in the two groups. Currently we designed a randomized, single-blinded controlled trial to compare the results of observation versus treatment with either *S. boulardii* or metronidazole on the duration of diarrhea and the duration of colonization in immunocompetent children with gastrointestinal symptoms and positive stool examination for *Blastocystis hominis* [45]. At the end of the first month, clinical cure rate was 94.4% in the *S. boulardii* group and 73.3% in the metronidazole group [45]. Clinical resolution and clearance of the organism may be due to the direct efficacy of the treatment on *B. hominis,* elimination of other undetected organisms, improved balance of the gut microflora or the combination of these factors.

Safety and adverse event data collected during clinical trials, when patients are closely monitored for problems associated with the investigational treatment, has documented a remarkable safety profile for *S. boulardii*. No fungemia has been reported in otherwise healthy adults and children receiving lyophilized preparations of this probiotic yeast for supportive therapy of diarrhea. The overall safety profile for *S. boulardii* is beneficial [23-41]. Sporadic cases of fungemia have been reported, and these occurred in patients with severe general or intestinal disease who had an indwelling catheter (this is a contraindication to the use of *S. boulardii*). Fungemia has only been reported in severely ill patients, including patients in intensive care units, patients who are mechanically ventilated, patients receiving broad-spectrum antibiotics through a central venous catheter or immunocompromised adult patients. Translocation from the gastrointestinal tract to the systemic circulation has not been reported. There is indeed confusion between fungemia with *S. boulardii* and *S. cerevisiae* and identification of the *S. boulardii* strain is difficult. Once the diagnosis is made, fungemia with *S. boulardii* can effectively be treated with antimycotic medication. *S. boulardii* does not persist 3 – 5 days after oral ingestion is discontinued, so persistence is not a concern [13,15,19,46,47].

The mechanisms of action of *S. boulardii* have been extensively investigated. It depends mainly on the inhibition of adhesion of pathogens, enhanced mucosal integrity, beneficial effects on the dysregulated immune response, production of antimicrobial substances, intestinal receptor modification, inhibition of some bacterial toxins, anti-inflammatory effects and effects on the intestinal mucosa such as trophic effects on the brush border. Most of these effects have been demonstrated in experimental studies, with only a few clinical studies having investigated them [16-19,48].

Because treatment can shorten the duration of diarrhea and reduce the length of hospital stay, there is probably a social and economic benefit of biotherapeutic treatment in adjunction to ORS in acute infectious gastroenteritis in children. It may seem that shortening the duration of diarrhea by 1 day or so is not a major health benefit. However, considering the high morbidity of infectious diarrhea, a reduction even of this order could afford considerable savings in terms of loss of working days and direct health costs. Furthermore, it should be considered that probiotics may reduce the risk of spreading infection by shortening the duration of diarrhea and decreasing the volume of watery stool output. The shortened duration of diarrhea and the reduction in hospital stay result in a social and economic benefit. In our current study, performed in Turkey, adding *S. boulardii* to the treatment of all rotavirus-related diarrhea in children < 5 years of age resulted in a 10% decrease in the total budget related to diarrhea and saved $32 (US) per patient [49]. There are some limitations to this analysis. Any meta-analysis is only as good as the constituent studies. In this meta-analysis, the trials that were included are significantly heterogeneous. Some trials included in our analysis had potential methodological limitations, including inadequate allocation concealment, no ITT analysis and no blinding. Furthermore, a small sample size was used in some trials, and different definitions of diarrhea were used in different trials.

5. Expert opinion

In May 2008, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the European Society of Paediatric Infectious Diseases Expert Working Group stated that because there is no evidence of efficacy for many probiotic preparations, only probiotic strains with *proven clinical efficacy* and in appropriate dosage are recommended as an adjunct for the management of children with acute gastroenteritis to rehydration therapy. Based on meta-analysis of properly designed RCTs of appropriate size, there is a strong level of evidence for the efficacy for treatment with LGG and *S. boulardii* [8]. World Gastroenterology Organization published online their recommendations about probiotic in treatment of acute diarrhea at October 2011. According to their evident-based recommendation, *S. boulardii and L. reuteri ATCC 55730, L. rhamnosus GG, L. casei DN-114 001* are useful in reducing the severity and duration (approximately 1 day) of acute infectious diarrhea in children and they pointed that probiotics are safe and effective, mechanism of action are strain specific and the timing of administration is also of importance [11]. In November 2011, Floch *et al.* [14] recently published recommendations of probiotic use. Regarding to *S. boulardii* effectiveness, they showed that level of evidence for effectiveness is A for childhood infectious diarrhea treatment, B for prevention of diarrhea and A for prevention of antibiotic-associated diarrhea.

There have been many double-blinded, randomized, placebo-controlled studies of *S. boulardii*, and well-conducted meta-analyses are now available about the use of *S. boulardii* in the treatment of acute diarrhea due to viral, bacterial and protozoan causes. *S. boulardii* can reduce the duration of diarrhea by approximately 1 day, shorten the initial phase of

watery stools and decrease the length of hospital stay. These results have been replicated worldwide, including in developing countries. This systematic review and meta-analysis of the efficacy of *S. boulardii* in the treatment of acute infectious diarrhea in infants and children concluded that there is strong evidence that this probiotic has a clinically significant benefit in the treatment of acute infectious diarrhea in infants and children, whatever the cause (viral, bacterial or protozoan). This benefit has been shown in developed and developing countries. *S. boulardii* appears to be effective in the treatment of viral, bacterial and protozoan-induced diarrhea. Therefore, *S. boulardii* is a potential add-on therapy in acute gastroenteritis. *S. boulardii* is safe for administration to children with acute diarrhea. Further randomized clinical trials are needed to test this therapy in specific groups, including norovirus-induced diarrhea, bacterial diarrhea and adult diarrhea. Cost-effectiveness analysis should be also performed in different countries.

Declaration of interest

Dinleyici has served as a speaker for Biocodex Turkey and GlaxoSmithKline. Y Vandenplas is a consultant for Biocodex and United Pharmaceuticals. M Ozen has served as a speker for Ferrosan Turkey. This manuscript has been evaluated by American Journal Experts for language and grammatical errors. The authors declare no conflict of interest to industry about the preparation of this article.

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