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Saccharomyces boulardii CNCM I-745 in different clinical conditions

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Introduction: Saccharomyces boulardii is a well-known probiotic worldwide, and there are numerous studies including experimental and clinical trials in children and adults by the use of S. boulardii.

Areas covered: The objective of the present report is to provide an update on the evidence for the efficacy of S. boulardii CNCM I-745 in different clinical conditions. Saccharomyces boulardii is one of the best-studied probiotics in acute gastroenteritis (AGE) and is shown to be safe and to reduce the duration of diarrhea and hospitalization by about 1 day. Saccharomyces boulardii is one of the recommended probiotics for AGE in children by European Society of Paediatric Infectious Diseases and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Saccharomyces boulardii is also a recommended probiotic for the prevention of antibiotic-associated diarrhea (AAD), and a recent study showed promising results for the treatment of AAD in children. There is insufficient evidence to recommend the long-term use of S. boulardii in patients with irritable bowel syndrome. Although some clinical studies showed positive effects of S. boulardii on inflammation, there is no clinical evidence that S. boulardii is useful in inflammatory bowel disease. Saccharomyces boulardii could be used in patients needing Helicobacter pylori eradication because the S. boulardii improves compliance, decreases the side effects and moderately increases the eradication rate. There are new promising results (improving feeding tolerance, shorten the course of hyperbilirubinemia), but we do still not recommend the routine use of S. boulardii in newborns.

Expert opinion: Saccharomyces boulardii CNCM I-745 is a good example for the statement that each probiotic needs to be taxonomically characterized and its efficacy and safety should be documented individually in different clinical settings.

Keywords: antibiotic-associated diarrhea, diarrhea, probiotics, Saccharomyces boulardii, Saccharomyces boulardii CNCM I-745


1. Introduction

Saccharomyces boulardii is non-pathogenic yeast isolated from tropical fruit such as lychee and mangosteen by the French microbiologist Henri Boulard [1]. Although closely related to Saccharomyces cerevisiae, S. boulardii has definitively different taxonomic, physiological, metabolic and genetic characteristics. Microsatellite polymorphism analysis and retrotransposon hybridization analyses showed that S. boulardii has a unique and specific microsatellite allele that differs from S. cerevisiae [1]. Although yeast accounts for a minority (< 0.1%) of the microflora, they are 10 times larger than bacteria and may represent a significant stearic hindrance for bacteria. The presence of yeast in different locations such as stomach and colon...

2. Acute infectious diarrhea in children

Acute infectious diarrhea is a well-studied clinical condition with *S. boulardii* in different settings in developing and developed countries [6-23]. We previously published a systematic review and meta-analysis about the use of *S. boulardii* in patients with acute infectious diarrhea [24]. According to 11 randomized controlled trials (RCTs) (n = 1306 children, 651 in the *S. boulardii* group and 655 controls), *S. boulardii* significantly reduces the duration of diarrhea with approximately 24 h (-0.99 days [95% CI: -1.40 to -0.58]). *Saccharomyces boulardii* also reduced the duration of hospitalization with approximately 20 h (~ -20 h, 95% CI: -1.14 to -0.54). Based on the results of nine RCTs involving 1128 children, *S. boulardii* significantly (48% reduction) reduced the risk of diarrhea on the third day (RR: 0.52; 95% CI: 0.42 – 0.65). The mean number of stools started to decrease at Day 2, and a significant reduction of the number of stools is reported on Days 3 and 4 [24]. According to the studies included in this review, there is strong evidence that this probiotic has a clinically significant benefit, whatever the cause (viral, bacterial, protozoan) of the gastroenteritis, including in developing countries. *Saccharomyces boulardii* is safe in children with acute diarrhea, and adverse effects associated with *S. boulardii* were not reported in any of these RCTs [24]. Furthermore, the shortened duration of diarrhea and the reduction in hospital stay result in social and economic benefits; therefore, *S. boulardii* is a potential therapeutic option in acute gastroenteritis (AGE) [25].

In addition to the reduction of duration of diarrhea and hospitalization, there are some promising end points about the use of *S. boulardii* in acute infectious diarrhea. Kurugol and Koturoglu [10] showed effects of *S. boulardii* for the reduction of persistent diarrhea lasting > 14 days without statistical significance. Villarruel et al. [13] also showed that incidence of persistent diarrhea > 7 days was lower in children who received *S. boulardii* compared with placebo (7 vs 27%). Also, Billoo et al. [11] showed a reduction in the recurrence of new episodes of diarrhea in *S. boulardii* group. Riaz et al. [23] showed that mean total oral rehydration solution (ORS) intake was significantly lower in the group with diarrhea treated with *S. boulardii* compared with placebo.

*Saccharomyces boulardii* with metronidazole in adult patients with giardiasis has beneficial effect on the resolution of diarrhea as well as on the clearance the *Giardia* cysts [12]. Like giardiasis, *S. boulardii* with metronidazole significantly shortened the duration of bloody diarrhea and total duration of diarrhea compared to metronidazole alone in patients with amebiasis and enhances clearance of cysts [9,17]. Contrary to these results, however, Savas-Erdeve et al. [18] showed no effect of *S. boulardii* added to antibiotic treatment for amebiasis-associated acute diarrhea in children. Currently, our group showed that *S. boulardii* has beneficial effects of patients with gastrointestinal complaints related with *Blastocystis hominis* [26].

There are numerous proposed mechanisms of action of *S. boulardii* in acute infectious diarrhea [4,27-29]. These actions have been identified to be directed towards the host and/or against the microorganisms. *Saccharomyces boulardii* plays a role in the regulation of intestinal microbial homeostasis and stabilization of the barrier function. *Saccharomyces boulardii* may also interfere with the ability of pathogens to colonize and infect the mucosa. Modulation of local and systemic immune responses is the other key mechanism against infectious diseases. Decreased expression of pro-inflammatory cytokines and increased expression of the anti-inflammatory cytokine IL-10 may also account for the beneficial effect of the yeast. *Saccharomyces boulardii* reduces mucositis, restores fluid transport pathways, secretes mitogenic factors that enhance cell restitution, enhance release of brush border membrane enzymes, releases polyamines, restores normal...
levels of colonic short-chain fatty acids (SCFAs) and strengthens enterocyte tight junctions [4,27-29]. Daily administration of S. boulardii results in detectable levels of live yeast through the gastrointestinal tract, and a stable concentration is reached in 3 days. These stable concentrations might be related with the peak clinical efficacy on diarrhea, which are seen at Day 3 of intervention [1,27]. Saccharomyces boulardii also inhibits the growth of bacteria and parasites, neutralizes the bacterial virulence factors, suppresses the host cell adherence that interferes with bacterial colonization and produces enzyme and proteins against bacteria [4,27-29]. For amebiasis, proposed mechanism for S. boulardii enhances the mucosal immune response and secretory IgA intestinal levels [30]. In 2014, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Diseases (ESPID) published their current recommendations in children with AGE. They highlighted that active treatment with probiotics, in adjunct to ORS, is effective in reducing the duration and intensity of symptoms of gastroenteritis. Selected probiotics can be used in children with AGE (recommendation at A1 level). According to this guideline, S. boulardii and Lactobacillus GG should be considered in the management of children with AGE as an adjunct to rehydration therapy with A1 level of evidence [31].

3. Antibiotic-associated diarrhea

In the general population, the incidence of antibiotic-associated diarrhea (AAD) ranges from 5 to 62% (11 – 40% in children), between the initiation of therapy and up to 2 months after the end of treatment [32,33]. There are randomized controlled clinical trials about the effects of S. boulardii on the prevention of AAD in children. Saccharomyces boulardii (250 mg/day) had a lower prevalence of diarrhea occurring during or up to 2 weeks after the antibiotic therapy in children with otitis media and/or respiratory tract infection. Saccharomyces boulardii also reduced the risk of AAD, which is caused either by Clostridium difficile or of unknown etiology compared with placebo [34]. Another RCT showed that S. boulardii had a reduced risk of diarrhea (6.2 vs 18%, RR 0.3; 95% CI 0.2 – 0.5) in children receiving ampicillin-sulbactam or azithromycin [35]. Currently, Shan et al. [36] showed that 5 days of S. boulardii treatment have beneficial effects for AAD treatment (in lower stool frequency and shorter duration of diarrhea) as well as prevention of AAD [36]. This study shows promising results for the prevention of AAD in children as well as the treatment of AAD.

In adults, S. boulardii showed significant efficacy for the prevention of AAD [1]. McFarland et al. [37] showed significantly fewer patients developed AAD with the β-lactam antibiotics plus S. boulardii [37]. Surawicz et al. [38] showed that only 9.5% of those randomized to S. boulardii (receiving the duration of therapy and plus an additional 2 weeks) developed AAD compared with 21.8% of those on placebo. Prevention of AAD with S. Boulardii has also been shown in studies performing in adult’s patients with Helicobacter pylori infection [39-41]. In a meta-analysis of published RCTs about S. boulardii’s effect on the prevention of AAD in adults, S. boulardii was significantly protective for AAD with a pooled relative risk of 0.47 (95% CI 0.35 – 0.63, p < 0.001) and the number need to treat was 10 [1].

Probiotics may also offer promise as an adjunctive therapy for C. difficile infection. Recurrence of C. difficile infection rate was significantly lower in patients receiving S. boulardii, and strongest effect was found in recurrent C. difficile infections [42]. In patients with recurrent C. difficile disease, significantly reduced recurrence rate of C. difficile disease and completely cleared C. difficile toxin from the colon were observed in patients receiving high-dose vancomycin and S. boulardii treatment [38].

Luminal actions and antimicrobial toxins of S. boulardii may play a role in the prevention of AAD [1,27]. Saccharomyces boulardii is naturally resistant to antibiotics. Saccharomyces boulardii levels are higher in patients with disturbed intestinal microbiota (due to antibiotic exposure) compared to patients without antibiotic exposure [43]. Reduction of gut translocation of pathogen is one of the key actions for maintenance of intestinal balance. Saccharomyces boulardii restores normal levels of colonic SCFAs, and this is related with the prevention of AAD. When S. boulardii is given to antibiotic-exposed mice or patients with diarrhea, normal microbiota is re-established rapidly. Saccharomyces boulardii inhibits the toxin’s receptor-binding sites and stimulates antibody production against C. difficile toxin A and produces a serine protease that cleaves C. difficile toxin. Saccharomyces boulardii inhibits IL-8 production and activation of the MAP kinases Erk1/2 and JNK/SAPK induced by C. difficile toxin A in human colonocytes. The potential effect of S. boulardii against the recurrence of C. difficile infection might be related with these effects [1,27,44].

3.1 HIV-related diarrhea

HIV infection results in gastrointestinal damage, microbial translocation and diarrhea. Saint Marc et al. [45] showed that 61% of HIV-infected individuals given S. boulardii had resolution of diarrhea compared with only 12% in the control group. No patient developed fungemia.

3.2 Helicobacter pylori

Addition of S. boulardii to standard therapy showed increased H. pylori eradication rate (statistically significant or not) and clearly reduced the adverse effect related with eradication therapy [46-49]. Hurduc et al. [47] performed a RCT in H. pylori-positive symptomatic children of 3 – 18 years, and they showed that, H. pylori eradication rate was 93.3% in the S. boulardii group, compared with 80.9% in the control group, without a statistical significance; however, the incidence of side effects was reduced in the S. boulardii group. Meta-analysis (five RCTs including 1307 participants) showed that S. boulardii given together with triple therapy significantly increased the eradication rate of H. pylori infection and reduced the risk of adverse effects (11.4% lower incidence), particularly of...
diarrhea. There was no influence on epigastric pain, taste disturbance, dry mouth, nausea, abdominal gas or bloating. *Saccharomyces boulardii* resulted in a 9% better eradication rate, and the number needed to treat was 11 [46]. *Saccharomyces boulardii* treatment alters the structure of *H. pylori* [50]. The effects of *S. boulardii* on the *H. pylori* eradication treatment side effects are similar with the prevention of AAD.

4. Traveler's diarrhea

McFarland included 12 RCTs with various probiotics (including *S. boulardii*) in the latest meta-analysis on the prevention of traveler's diarrhea (TD), showing a significant reduction of the risk of TD [1] Kollaritsch *et al.* [51] showed reduced incidence of TD in travelers receiving *S. boulardii* (1 g/day) comparing with placebo (29 vs 39%). The efficacy of probiotics on the prevention of TD is related to the strain and dose, travel destination and duration of the travel. There are no well-designed studies in the treatment of TD.

5. Crohn’s disease and ulcerative colitis

The first study on *S. boulardii* in 20 patients with Crohn's disease (CD) was published by Plein and Hotz in 1993 [52], and they showed that *S. boulardii* (250 mg twice a day, for 2 weeks in addition to standard treatment) reduced frequency of bowel movement and disease activity index [52]. Patients with CD in clinical remission, clinical relapse rate was higher in patients receiving mesalazine alone comparing to mesalamine plus *S. boulardii* (37.5 vs 6.25%) [53]. Garcia-Vilela *et al.* [54] showed that patients with CD in remission present alterations in the integrity of the intestinal mucosal barrier; *S. boulardii* added to baseline therapy decreased intestinal permeability, even though complete normalization was not achieved. A Cochrane analysis published in 2006 concluded that *S. boulardii* added to maintenance therapy resulted in a non-statistically significant decrease in relapses of CD compared to maintenance alone [55]. In 2011, Thomas *et al.* [56] showed that *S. boulardii* significantly decreased the frequency of CD40-, CD80- and CD197 (chemokine receptor-7)-expressing inflammatory bowel disease dendritic cells and reduced the secretion of TNF-α and IL-6, while increasing IL-8. They showed synergistic mechanisms between control of inflammation (inhibition of T-cell costimulation and inflammation-associated migration and mobilization of dendritic cells) and promotion of epithelial restitution induced by *S. boulardii*. Currently, Bourreille *et al.* [57] performed a large RCT to evaluate the effects of *S. boulardii* (1 g/day) given during 52 weeks in patients with CD in remission during therapy with steroids or aminosalicylates. The percentage of patient in remission after 1 year was similar (47.5 vs 53.2%) as well as the median time when relapse occurred. There were also no differences in CD activity index, erythrocyte sedimentation rate and C-reactive protein level. Effects of *S. boulardii* in adult patients with ulcerative colitis have been performed with one study, *S. boulardii* (250 mg thrice a day) for 1 month in addition to mesalazine maintenance treatment showed a clinically and endoscopically proven remission [58].

6. Newborn period

*Saccharomyces boulardii* is not recommended for routinely use during the newborn period (up to the age of 1 month). However, some clinical trials have been performed in newborns [59-64]. Regarding six published studies performing in newborns, *S. boulardii* was safe and well-tolerated. *Saccharomyces boulardii* has no effect on incidence and severity of necrotizing enterocolitis (NEC) among newborn infants, with a gestational age less than 32 weeks and a birth weight below 1500 g [60,61]. Demirel *et al.* showed that *S. boulardii* (250 mg once a day) in very low birth weight (VLBW) infants (gestational age of ≤ 32 weeks and birth weight of < 1500 g) reduced the duration of phototherapy and feeding intolerance. The authors hypothesized that *S. boulardii* improved feeding tolerance by suppressing the reabsorption of bilirubin into the enterohepatic circulation [62]. However, contrary to this study, current study showed that *S. boulardii* did not influence the clinical course of indirect hyperbilirubinemia [63]. *Saccharomyces boulardii* administration in VLBW infants resulted in reducing fungal colonization and invasive fungal infection, and *S. boulardii* was as effective as nystatin [64].

7. Irritable bowel syndrome

Already in 1983, Maupas *et al.* [65] showed that 4 weeks of *S. boulardii* in patients with irritable bowel syndrome (IBS) lead to a significant decrease in the daily number of stool and improvement in clinical symptoms related with IBS. Bafutto *et al.* [66] showed that *S. boulardii* alone or with mesalamine lowered symptom score in adult patients with diarrhea-dominant IBS. However, Kabir *et al.*’s study [67] in adult patients with diarrhea-dominant IBS, *S. boulardii* did not result in any improvement. *Saccharomyces boulardii* improved quality of life better than placebo but was not superior to individual symptoms in patients with diarrhea-predominant IBS or mixed-type IBS. *Saccharomyces boulardii* has potential effect on the overall improvement in quality of life, and abdominal discomfort, mucus in stool, and passage of gas were significantly improved. [68]. Potential mechanism of action of *S. boulardii* in IBS is restoration of intestinal microbiota.

8. Expert opinion

Numerous clinical studies on probiotics are published every year, and there is a large amount of information on probiotics in different clinical conditions. *Saccharomyces boulardii* CNCM I-745 is one of the better known and studied probiotic strains, with dose-efficacy data in different clinical conditions (Table 1). *Saccharomyces boulardii* is shown to be safe and
Table 1. Summary of published studies with *Saccharomyces boulardii* CNCM I-745 regarding to design, enrollment number, condition, end point and results.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study description</th>
<th>Age groups</th>
<th>S. boulardii versus comparators</th>
<th>End point</th>
<th>Results and notes</th>
</tr>
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<tbody>
<tr>
<td>Dinleyici et al. (2012) [24]</td>
<td>Systematic review and meta-analysis Including studies from different countries</td>
<td>11 RCTs (n = 1306 children, 651 in the S. boulardii group and 655 controls)</td>
<td>S. boulardii versus comparators</td>
<td>Duration of diarrhea, duration of hospitalization, presence of diarrhea at the third day of intervention</td>
<td><em>S. boulardii</em> significantly reduces the duration of diarrhea with ~24 h (the pooled weighted mean difference was -0.99 days (95% CI: -1.40 to -0.58) with a fixed model. <em>S. boulardii</em> reduced the duration of hospitalization with ~20 h (449 children). <em>S. boulardii</em> significantly reduced the risk of diarrhea on the third day (~48% reduction; RR: 0.52; 95% CI: 0.42 – 0.65). The mean number of stools started to decrease at Day 2 and a significant reduction of the number of stools is reported on Days 3 and 4. Adverse effects associated with <em>S. boulardii</em> were not reported in any of these RCTs.</td>
</tr>
<tr>
<td>Kurugol and Koturoglu (2005) [10]</td>
<td>Randomized, double-blind controlled study Turkey</td>
<td>200 children 3 months to 7 years old 41.5% rotavirus</td>
<td><em>S. boulardii</em> 250 mg (n = 100) versus placebo (n = 100) for 5 days</td>
<td>The duration of diarrhea and the occurrence of side effects</td>
<td>The duration of diarrhea significantly decreased in <em>S. boulardii</em> group compared with placebo. The number of stools showed significant reduction in the <em>S. boulardii</em> group on Days 2 and 3. Duration of hospital stay was shorter in the <em>S. boulardii</em> group. The diarrhea persisted for &gt;14 days in 4% of patients in the placebo group; only 1% of patients in <em>S. boulardii</em> group.</td>
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<tr>
<td>Villarruel et al. (2007) [13]</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>88 children (72 children evaluated at first month) 3 – 24 months Acute diarrhea</td>
<td><em>S. boulardii</em> 250 – 500 mg (n = 44) daily versus placebo (n = 44)</td>
<td>Number of stools, diarrhea lasting for &gt;7 days Duration of diarrhea and the effect when</td>
<td>The total number of stools and the number of watery stools passed on the fourth and seventh days were significantly lower in the <em>S. boulardii</em> group.</td>
</tr>
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</table>

AAD: Antibiotic-associated diarrhea; b.i.d.: Twice daily; CD: Crohn's disease; IBS: Irritable bowel syndrome; ORS: Oral rehydration solution; RCTs: Randomized controlled trials; t.i.d.: Three times a day; VLBWs: Very low birth weights.
Table 1. Summary of published studies with *Saccharomyces boulardii* CNCM I-745 regarding to design, enrollment number, condition, end point and results (continued).

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<td>Billoo et al. (2006) [11]</td>
<td>Randomized controlled study Pakistan</td>
<td>100 children 2 months to 12 years 16 - 20% rotavirus 12 - 26% bacterial cause</td>
<td>S. boulardii 500 mg plus WHO-CDD diarrhea protocol (n = 50) versus WHO-CDD diarrhea protocol (n = 50)</td>
<td>Number of stools, mean duration of diarrhea, follow-up for diarrhea</td>
<td>Treatment was started within 48 h after the onset of diarrhea was significantly reduced in the S. boulardii group (4.7 vs 6.16 days, p &lt; 0.05) A statistically significant decrease (p &lt; 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 after the onset of 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 = 0.0001). S. boulardii also reduced the number of episodes of diarrhea by 50% in the subsequent 2 months (p = 0.04) Duration of post-intervention diarrhea was shorter in S. boulardii group (52.85 ± 24.6 h) compared to placebo group (64.61 ± 30.9 h). The time of appearance of first semi-formed stool was earlier in S. boulardii group than placebo. Total ORS consumption was lower in S. boulardii group Median clearance of symptoms was earlier in the S. boulardii plus metronidazole group (24 h) than in the metronidazole-alone group (30 h); however, the</td>
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<td>Mansour-Ghanei et al. (2003) [9]</td>
<td>Double-blind randomized controlled study Iran</td>
<td>54 adults</td>
<td>Acute mucous bloody diarrhea due to amebiasis</td>
<td>Metronidazole 750 mg and iodoquinol 650 mg/day for 10 days or the same medication plus S. boulardii 250 mg orally</td>
<td>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 the fever decreased by almost 50% in the S. boulardii group. Giardia lamblia cysts were not detected in the S. boulardii group but were detected in six cases (three symptomatic) in the metronidazole-alone group. Amebic cysts were not found in the stool specimens of patients receiving S. boulardii compared with 18.5% of individuals in the control group.</td>
</tr>
<tr>
<td>Dinleyici et al. (2009) [17]</td>
<td>Prospective, randomized, open-label study Turkey</td>
<td>50 children</td>
<td>Acute bloody diarrhea due to amebiasis</td>
<td>Metronidazole (n = 25) versus metronidazole plus S. boulardii (n = 25)</td>
<td>Primary: duration of bloody diarrhea and microscopic detection of blood in the stools. Secondary: duration of diarrhea, follow-up microscopic examination of amebiasis. The duration of bloody diarrhea was significantly shorter in S. boulardii group (72 h vs 42 h, p &lt; 0.001). Cessation of diarrhea in the S. boulardii group occurred at 45 and at 74 h in metronidazole-alone group, (p = 0.0001). After 72 h of treatment, the frequency of bloody diarrhea (44 vs 11%) and diarrhea (76 vs 44%) were lower in the S. boulardii group plus metronidazole group.</td>
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<td>Savas-Erdeve et al. (2009) [18]</td>
<td>Open-prospective study</td>
<td>90 children</td>
<td>1 – 15 years Entamoeba</td>
<td>Metronidazole versus metronidazole plus lyophilized S. boulardii for 10 days</td>
<td>Duration of acute diarrhea, presence of bloody diarrhea; resolution time of acute diarrhea and bloody diarrhea and the resolution time of symptoms including vomiting.</td>
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<td>Kotowska <em>et al.</em> (2005) [34]</td>
<td>Randomized, double-blind, placebo-controlled clinical trial</td>
<td>269 children 6 months to 14 years</td>
<td>250 mg of <em>S. boulardii</em> or a placebo</td>
<td>vomiting, abdominal pain and fever during the treatment</td>
<td>The frequencies of diarrhea and AAD, the need for discontinuation of the antibiotic treatment, hospitalization to manage the diarrhea, or intravenous rehydration; and adverse events. The addition of <em>S. boulardii</em> to antibiotic therapy reduced the risk of diarrhea (7.5 vs 23%); the number need to treat was 7. <em>S. boulardii</em> also reduced the risk of AAD (3.4 vs 17.3%, the number need to treat was 8). The risk of documented <em>Clostridium difficile</em> diarrhea was also lower in the <em>S. boulardii</em> group with the borderline significance. There was no need for discontinuation of antibiotic treatment, hospital treatment because of diarrhea in the out-patients, or intravenous rehydration in any of the study groups. The <em>S. boulardii</em> was well tolerated, and no adverse events were reported.</td>
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<td>Erdeve <em>et al.</em> (2004) [35]</td>
<td>Prospective, open-label study</td>
<td>653 children 1 - 15 years</td>
<td>Sulbactam-ampicillin (SAM) alone, both SAM and <em>S. boulardii</em>; azithromycin, azithromycin and <em>S. boulardii</em></td>
<td>Watery diarrhea during or after the 10 days of treatment</td>
<td>AAD was seen in 18.9% of children receiving an antibiotic without the probiotic, and 5.7% who received both the probiotic and the antibiotic (p &lt; 0.05). Children receiving SAM where <em>S. boulardii</em> use was found to be significant, the use of <em>S. boulardii</em> decreased the diarrhea rate from 32.3 - 11.4% in the</td>
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<tr>
<td>Shan et al. (2013) [36]</td>
<td>Two-phase, open, randomized controlled clinical trial China</td>
<td>333 hospitalized children with lower respiratory tract infection China</td>
<td><em>S. boulardii</em> 500 mg/day with antibiotics, n = 167 or received antibiotic alone (n = 166). Children who developed diarrhea in antibiotics alone were randomly allocated to receive <em>S. boulardii</em> with ORS and ORS alone</td>
<td>Diarrhea during at least 2 days, occurring during treatment and/or up to 2 weeks after antibiotic therapy had stopped. During the second phase of study, duration of diarrhea was evaluated</td>
<td><em>S. boulardii</em> reduced the risk of AAD (4.3 vs 19.4%). When children receiving antibiotics alone developed diarrhea, <em>S. boulardii</em> treatment during 5 days resulted in lower stool frequency (p &lt; 0.05), higher recovery rate (p &lt; 0.001) and the mean duration of diarrhea was shorter (2.31 ± 0.95 vs 8.97 ± 1.07 days; p &lt; 0.001).</td>
</tr>
<tr>
<td>McFarland et al. (1995) [38]</td>
<td>Double-blind, placebo-controlled, parallel group study United States</td>
<td>193 patients High risk group for hospitalized patients</td>
<td><em>S. boulardii</em> or placebo (1 g/day) was given within 72 h of the start of the β-lactam antibiotics and continued until 3 days after the antibiotic was discontinued</td>
<td>AAD prevalence during 7 weeks follow-up period.</td>
<td>*AAD rate was lower in <em>S. boulardii</em> group compared with the placebo (7.2 vs 14.6%, p = 0.02). The efficacy of <em>S. boulardii</em> for the prevention of AAD was 51%</td>
</tr>
<tr>
<td>Surawicz et al. (1989) [37]</td>
<td>Prospective, double-blind, placebo-controlled RCT United States</td>
<td>180 patients</td>
<td><em>S. boulardii</em> (receiving the duration of antibiotic therapy and plus an additional 2 weeks)</td>
<td>AAD prevalence, related risk factors, prevalence of <em>C. difficile</em> infection</td>
<td>The rate of AAD was lower in <em>S. boulardii</em> group compared with placebo group (9.5 vs 22%, p &lt; 0.05). Risk factors found to be associated with AAD were multiple antibiotic combinations and tube feeding.</td>
</tr>
<tr>
<td>Duman et al. (2005) [39]</td>
<td>Multi-center, prospective clinical trial Turkey</td>
<td>376 adult patients with peptic ulcer disease or non-ulcer dyspepsia</td>
<td><em>S. boulardii</em> 500 mg twice daily or no treatment with clarithromycin, amoxicillin and omeprazole for <em>Helicobacter pylori</em> eradication for 14 days</td>
<td>Development of diarrhea during (treatment period) or within 4 weeks after treatment</td>
<td>AAD rate during the antibiotic therapy was lower in <em>S. boulardii</em> group compared to control group (5.9 vs 11.5%, p = 0.049). During the 4 weeks of follow-up period, rate of AAD was lower in <em>S. boulardii</em> group (1.0 vs 3.8%, p = 0.09)</td>
</tr>
</tbody>
</table>

AAD: Antibiotic-associated diarrhea; b.i.d.: Twice daily; CD: Crohn's disease; IBS: Irritable bowel syndrome; ORS: Oral rehydration solution; RCTs: Randomized controlled trials; t.i.d.: Three times a day; VLBWs: Very low birth weights.
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<tr>
<td>Cindoruk et al.</td>
<td>Prospective, randomized, placebo-controlled clinical trial</td>
<td>Turkey</td>
<td>124 patients with <em>H. pylori</em> infection</td>
<td>14 days of triple therapy (clarithromycin, amoxicillin, lansoprazole) were randomly assigned to <em>S. boulardii</em> or placebo</td>
<td>Dyspeptic symptoms and side effects of treatment 9 (14.5%) patients in the <em>S. boulardii</em> group and 19 (30.6%) patients in the placebo group experienced diarrhea (<em>p</em> &lt; 0.05) A significant decrease in recurrences was observed in patients treated with high-dose vancomycin (2 g/day) and <em>S. boulardii</em> (16.7%), compared to high-dose vancomycin and placebo (50%) Patients treated with <em>S. boulardii</em> had a significantly lower relative risk of CDD recurrence compared with placebo. The efficacy of <em>S. boulardii</em> was significant in patients with recurrent CDD, but not in patients with initial CDD</td>
</tr>
<tr>
<td>Surawicz et al.</td>
<td>Prospective, randomized, placebo-controlled clinical trial</td>
<td>United States</td>
<td>124 patients</td>
<td>Standard antibiotic for 10 days and then added either <em>S. boulardii</em> (1 g/day for 28 days) or placebo</td>
<td>Recurrence of <em>C. difficile</em> infection</td>
</tr>
<tr>
<td>McFarland et al.</td>
<td>Double-blind, randomized, placebo-controlled, parallel-group intervention study</td>
<td>United States</td>
<td>124 patients</td>
<td>Patients with active <em>C. difficile</em> disease</td>
<td>Recurrence of active CDD disease</td>
</tr>
<tr>
<td><em>H. pylori</em> infection</td>
<td>Meta-analysis 5 randomized controlled clinical trials before June 2010</td>
<td>1307 patients</td>
<td><em>S. boulardii</em> versus comparators</td>
<td>Eradication rate for</td>
<td><em>S. boulardii</em> given along with triple therapy significantly increased the eradication rate (RR 1.13, 95% CI 1.05 – 1.21) and reduced the risk of overall <em>H. pylori</em> therapy-related adverse effects (RR: 0.47, 95% CI 0.32 – 0.69)</td>
</tr>
<tr>
<td>Hurduc et al.</td>
<td>Prospective, open-label clinical study</td>
<td>90 children</td>
<td>3 – 18 years</td>
<td>Standard triple eradication therapy (omeprazole/esomeprazole, amoxicillin and clarithromycin) with or without <em>S. boulardii</em> (250 mg b.i.d. for 4 weeks)</td>
<td>The eradication rate of <em>H. pylori</em></td>
</tr>
</tbody>
</table>

AAD: Antibiotic-associated diarrhea; b.i.d.: Twice daily; CD: Crohn’s disease; IBS: Irritable bowel syndrome; ORS: Oral rehydration solution; RCTs: Randomized controlled trials; t.i.d.: Three times a day; VLBWs: Very low birth weights.
Table 1. Summary of published studies with *Saccharomyces boulardii* CNCM I-745 regarding to design, enrollment number, condition, end point and results (continued).

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<tr>
<td>Song et al. (2010) [48]</td>
<td>Prospective, randomized clinical trial</td>
<td>991 patients</td>
<td>PPI-based 7-day triple therapy, triple therapy plus S. boulardii for 4 weeks, and triple therapy plus S. boulardii and mucoprotective agent</td>
<td>The eradication rate of <em>H. pylori</em></td>
<td>Eradication rate was higher in patient receiving S. boulardii (80.0 vs 71.6%). The frequency of side effects were also lower in S. boulardii group (14.5 vs 19.1%)</td>
<td></td>
</tr>
<tr>
<td>Ozdil et al. (2011) [49]</td>
<td>Prospective, randomized clinical trial Turkey</td>
<td>285 patients</td>
<td>Lansoprazole, clarithromycin, amoxicillin and S. boulardii 14 days</td>
<td>Eradication rate</td>
<td>Eradication rate was higher in S. boulardii plus esomeprazole, levofloxacin, amoxicillin group than esomeprazole, levofloxacin, amoxicillin group (89.1 vs 77.1%)</td>
<td></td>
</tr>
<tr>
<td>Plein and Hotz (1993) [52]</td>
<td>Randomized, single-center, double-blind, placebo-controlled pilot study</td>
<td>20 patients with established CD</td>
<td>S. boulardii 250 mg t.i.d. daily in 2 weeks in addition to the basic treatment</td>
<td>Disease activity index</td>
<td>The patients treated with S. boulardii showed a significant reduction in the frequency of bowel movements and disease activity index. Clinical relapse rate was 37.5% in mesalamine alone group, while 6.25% in mesalamine plus S. boulardii group. There was an improvement in intestinal permeability, with a decrease in the lactulose/mannitol ratio (<em>p</em> &lt; 0.001) in S. boulardii group.</td>
<td></td>
</tr>
<tr>
<td>Guslandi et al. (2000) [53]</td>
<td>Prospective, randomized controlled clinical trial Italy</td>
<td>32 patients with CD in clinical remission</td>
<td>Mesalamine (1 g t.i.d.) or mesalamine 1 g b.i.d. plus S. boulardii 1 g daily for 6 months</td>
<td>Clinical relapse rate</td>
<td>Clinical relapse rate was 37.5% in mesalamine alone group, while 6.25% in mesalamine plus S. boulardii group. There was an improvement in intestinal permeability, with a decrease in the lactulose/mannitol ratio (<em>p</em> &lt; 0.001) in S. boulardii group.</td>
<td></td>
</tr>
<tr>
<td>Garcia-Vilela et al. (2008) [54]</td>
<td>Prospective, placebo controlled clinical trial</td>
<td>34 patients with CD and 15 healthy controls</td>
<td>S. boulardii versus placebo</td>
<td>Intestinal permeability (lactulose/mannitol ratio)</td>
<td>clinical relapse rate was 37.5% in mesalamine alone group, while 6.25% in mesalamine plus S. boulardii group. There was an improvement in intestinal permeability, with a decrease in the lactulose/mannitol ratio (<em>p</em> &lt; 0.001) in S. boulardii group.</td>
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<tbody>
<tr>
<td>Bourreille et al. (2013) [57]</td>
<td>Randomized, placebo-controlled trial</td>
<td>165 patients with CD who achieved remission</td>
<td>S. boulardii (1 g/day) or placebo for 52 weeks</td>
<td>The primary end point: percentage of patients in remission at week 52. Secondary: time to relapse, Crohn's disease activity index scores, and changes in parameters of inflammation. Before and after treatment, as done by Rachmilewitz' Activity Index, showed persistent clinical remission (values &lt; 6).</td>
<td>S. boulardii is safe and well tolerated in CD, however has no beneficial effects for patients with CD in remission after steroid or salicylate therapies (relapse rate was 47.5% in S. boulardii group versus 53.2% in placebo group).</td>
</tr>
<tr>
<td>Guslandi et al. (2003) [58]</td>
<td>Case series</td>
<td>Italy</td>
<td>Left sided UC of mild-to-moderate degree, in remission after a course of oral steroids, intolerant to mesalamine, and unwilling to take immunosuppressive therapy. 6 patients 26 - 49 years</td>
<td>S. boulardii 500 mg in the morning plus rifaximine 400 mg in the evening for 3 months</td>
<td>Before and after treatment, as done by Rachmilewitz' Activity Index, showed persistent clinical remission (values &lt; 6). S. boulardii and rifaximin seemed capable of preventing early flare-up of UC.</td>
</tr>
<tr>
<td>Serce et al. (2013) [60]</td>
<td>Prospective, double-blind, placebo controlled trial</td>
<td>Turkey (≤ 32 GWs, ≤ 1500 g birth weight)</td>
<td>Feeding supplementation with S. boulardii 50 mg/kg every 12 h or placebo, starting with the first feed until discharged.</td>
<td>Necrotizing enterocolitis (NEC) or sepsis and NEC or death. Serum bilirubin levels were measured at 0, 24th, 48th, 72nd, and 96th h of phototherapy. The duration of phototherapy was not different between groups. S. boulardii did not influence the clinical course of indirect hyperbilirubinemia.</td>
<td>Incidence of stage ≥ 2 NEC or death and incidence of stage ≥ 2 NEC or late onset culture-proven sepsis was similar between the groups. The duration of phototherapy was not different between groups. S. boulardii did not influence the clinical course of indirect hyperbilirubinemia.</td>
</tr>
<tr>
<td>Serce et al. (2014) [63]</td>
<td>Prospective, double-blind, placebo controlled trial</td>
<td>Turkey</td>
<td>119 newborns 35 to 42 gestational weeks</td>
<td>Feeding supplementation with S. boulardii 125 mg every 12 h or placebo during phototherapy.</td>
<td>The primary outcomes were death or NEC (Bell's stage ≥ 2), and secondary outcomes were feeding intolerance and clinical or culture-proven sepsis. There was no significant difference in the incidence of death (3.7 vs 3.6%) or NEC (4.4 vs 5.1%) between the groups. Feeding intolerance and clinical sepsis were significantly lower in the S. boulardii group compared with control.</td>
</tr>
<tr>
<td>Demirel et al. (2013) [61]</td>
<td>Prospective, RCT</td>
<td>Turkey</td>
<td>271 newborns Newborns gestational age ≤ 32 weeks and birth weight ≤ 1500 g</td>
<td>S. boulardii 250 mg/Day versus none</td>
<td>The primary outcomes were death or NEC (Bell's stage ≥ 2), and secondary outcomes were feeding intolerance and clinical or culture-proven sepsis. There was no significant difference in the incidence of death (3.7 vs 3.6%) or NEC (4.4 vs 5.1%) between the groups. Feeding intolerance and clinical sepsis were significantly lower in the S. boulardii group compared with control.</td>
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<tbody>
<tr>
<td>Demirel et al. (2013) [64]</td>
<td>A prospective, randomized comparative study Turkey</td>
<td>181 newborns Gestational age of ≤ 32 weeks and birth weight of ≤ 1,500 g</td>
<td>S. boulardii versus nystatin</td>
<td>Prevention of fungal colonization and invasive fungal infections in VLBWs</td>
<td>Fungal colonization and infection rate was lower in S. boulardii group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feeding intolerance, clinical sepsis, and number of sepsis attacks were significantly lower in the S. boulardii group</td>
</tr>
<tr>
<td>Demirel et al. (2013) [62]</td>
<td>Prospective, randomized clinical trial Turkey</td>
<td>179 newborns Gestational age of ≤ 32 weeks and birth weight of ≤ 1500</td>
<td>S. boulardii 250 mg once a and the infants in the control group were fed without S. boulardii</td>
<td>Duration of phototherapy and levels of total bilirubin at the end of phototherapy</td>
<td>The duration of phototherapy was shorter in the S. boulardii group (1.9 ± 0.86 vs 2.6 ± 0.9 days, p = 0.00). Feeding intolerance was significantly lower in the study group than in the control group (20.9 vs 47.9%; p = 0.00)</td>
</tr>
<tr>
<td>Kabir et al. (2011) [67]</td>
<td>Randomized double blind placebo controlled clinical trial Bangladesh</td>
<td>35 patients diarrhoea predominant IBS and S. boulardii 250 mg or placebo twice daily orally for 1 month</td>
<td>S. boulardii 250 mg or placebo twice daily orally for 1 month</td>
<td>Symptom scoring system</td>
<td>No significant difference between the two groups was found in any of the parameters evaluated on any of the observation days Overall improvement in IBS-QOL was higher in S. boulardii group than placebo (15.4 vs 7.0%; p &lt; 0.05) S. boulardii was not superior for individual symptoms in patients</td>
</tr>
<tr>
<td>Choi et al. (2011) [68]</td>
<td>Prospective, randomized, double blind clinical trial</td>
<td>67 patients Diarrhea-predominant IBS or mixed-type IBS</td>
<td>S. boulardii 2 × 10^9 live cells as a daily dose or placebo for 4 weeks</td>
<td>Effects of S. boulardii on quality of life and IBS-related symptoms, bowel movement frequency, and stool consistency</td>
<td>Statistically significant reduction of symptom score after 30th day therapy in all groups: The improvement of the symptom score was greater with mesalazine alone or combined with S. boulardii as compared with S. boulardii treatment alone</td>
</tr>
<tr>
<td>Bafutto et al. (2013) [66]</td>
<td>Prospective clinical trial Brasil</td>
<td>53 patients 18 years or more IBS (diarrhea dominant) based on Rome III criteria</td>
<td>Mesalazine 800 mg t.i.d. for 30 days</td>
<td>Symptom evaluations at baseline and after treatment with a 4-point Likert scale including: stool frequency, stool form and consistency, abdominal pain and distension</td>
<td></td>
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to reduce the duration of diarrhea and hospitalization with about 1 day. Regarding current ESPGHAN/ESPID recommendation for AGE, *S. boulardii* is one of the recommended probiotics for AGE in children [31]. In AGE, further randomized clinical trials might be performed to test *S. boulardii* in specific groups, including norovirus-induced diarrhea, bacte-
riaria diarrhea and adult diarrhea. However, considering the high morbidity of infectious diarrhea, a reduction of the duration of diarrhea with 24 h will result in considerable savings in terms of loss of working days and direct health costs. Cost-effectiveness analyses of *S. boulardii* should be performed in different countries.

Antibiotics are very frequently prescribed drugs, especially in children. AAD is one of the important side effects, may also be delayed for up to 2 months after antibiotics are discontinued. *Saccharomyces boulardii* is one of the recommended probiotic for the prevention of AAD in children according to the Yale Workshop Group and the World Gastroenterology Organization has also recommended *S. boulardii* for prevention of AAD [60,70]. A recent study with *S. boulardii* for the treatment of AAD in children showed promising results. There are some studies showing no effect of probiotics on the prevention of AAD, and this might be related with short or no follow-up after antibiotic exposure. Cost-effectiveness analyses of *S. boulardii* as well as other probiotics should be also performed.

Regarding IBS, there are contradictory results for the use of *S. boulardii*. There is insufficient evidence to recommend the long-term use of *S. boulardii* in patients with IBS. The clinical severity and symptoms varies in patients with IBS. Further studies should be performed in patients with specific symptoms. Although *in vitro* research showed positive effects of *S. boulardii* on inflammation, there is no clinical evidence that *S. boulardii* reduces the incidence of flare-ups of inflammatory bowel disease (CD and ulcerative colitis) or prolongs the duration of remission. It is worthwhile to consider *S. boulardii* in patients needing *H. pylori* eradication because the yeast improves compliance, decreases the side effects and moderately increases the eradication rate.

*Saccharomyces boulardii* seems to improve feeding tolerance in VLBW infants and may shorten the course of hyperbiliru-
binemia. However, a preventive effect on NEC could not be shown. Because many preterm babies have venous lines, and because this is a contra-indication for *S. boulardii* administration, we still do not recommend the routine use of *S. boulardii* in newborns.

The mechanisms of action of *S. boulardii* have been well studied. Many aspects of these mechanisms are not different for *S. boulardii* than for other probiotics. However, some mechanisms are very specific for the yeast, such as the secretion of toxins specific against *Clostridium* and the tropic effects on the gastrointestinal mucosa induced by polyamines.

Currently published article “The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic” includes some criteria’s about the definition of ‘probiotic drug’s’ [71]. Claim for the probiotic drug was ‘Specific indication for treatment or prevention of disease’, and there are numerous clinical trials for the treatment of acute infectious diarrhea and the prevention of AAD. A defined strain of live microbe is a key feature of the definition, and all published articles which used in this review have been performed with *S. boulardii* CNCM I-745 (manufactured by Biocodex). ‘Proof of delivery of viable probiotic at efficacious dose at end of shelf-life’ is key definition criteria and should be described by manufacturers. ‘Risk–benefit assessment justifies use’ is other definition criteria and no adverse effects were observed in any of the clinical trials with *S. boulardii*, and *S. boulardii* is generally well tolerated. Saccharomyces fungemia is only reported in patients with immunocompromised condition or gastrointestinal disease, and presence of indwelling central venous catheter (major contradiction of *S. boulardii* use). Overall, *S. boulardii* is safe for use in otherwise healthy populations and fungemia with *S. boulardii* has not been reported. ‘Appropriate trials to meet regulatory standards for drugs’ is another definition criteria, and meta-analysis and systematic review of *S. boulardii* CNCM I-745 have been performed with the results of randomized controlled clinical trial (placebo or comparator agents) [71]. For all new indications, all probiotic strain including *S. boulardii* CNCM I-745 should be evaluated according to these criteria.

### Declaration of interest

This is an invited review from journal, and authors have no conflict of interest with industry for the preparation, writing and publication of this manuscript. EC Dinleyici is an International Advisory Board Member of Biocodex, M Ozen is a consultant and invited speaker for Pfizer Consumer Health, Y Vandenplas is a consultant for Biocodex and United Pharmaceuticals. A Kara declares no conflict of interest. The authors have no other relevant affiliations or financial involve-
ment with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.


Bibliography
Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.

This extensive review includes all clinical trials with Saccharomyces boulardii use in adults.

This review evaluated all clinical studies and showed reduced duration of diarrhea and hospitalization in patients with acute infectious diarrhea.

Saccharomyces boulardii CNCM I-745 in different clinical conditions


**Current European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/ESPID Evidence Based Guidelines Working Group for Probiotics and Prebiotics, recommended four probiotics for the treatment of acute infectious diarrhea in children at 2014; S. boulardii and LGG have A1 level of evidence.**


**This is the first study about the effect of treatment of antibiotic-associated diarrhea (AAD) in children with S. boulardii as well as prevention of AAD.**


Saccharomyces boulardii CNCM I-745 in different clinical conditions

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60. Serce O, Benzer D, Gursoy T, et al. 
Efficacy of Saccharomyces boulardii on necrotizing enterocolitis or sepsis in very low birth weight infants: a randomised controlled trial. Early Hum Dev 2013;89:1033-6


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Role of Saccharomyces boulardii in diarrhea predominant irritable bowel syndrome. Mymensingh Med J 2011;20:397-401

68. Choi CH, Jo SY, Park HJ, et al. 


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