

# Treatment of Acute Diarrhea With *Saccharomyces boulardii* in Infants

‡Naflesia B.O. Corrêa, \*Francisco J. Penna, †Fátima M.L.S. Lima, ‡Jacques R. Nicoli, and \*Luciano A.P. Filho

## ABSTRACT

**Objective:** The aim of the study was to determine whether an oral treatment with a commercial pharmaceutical product containing *Saccharomyces boulardii* would reduce the duration of diarrhea in infants with acute diarrhea.

**Patients and Methods:** In the present double-blind, placebo-controlled study, 186 infants, 6 to 48 months old and hospitalized within 72 hours after the onset of acute diarrhea in 2 hospitals in Goiânia, Goiás, Brazil, were randomly assigned to receive twice per day for 5 days 200 mg of a commercial pharmaceutical product containing  $4 \times 10^9$  viable cells of *S. boulardii* or a placebo. Stool samples were submitted to search for rotavirus. Among the 176 infants who completed the trial, those treated with *S. boulardii* (90) showed a reduction in diarrhea duration ( $P < 0.05$ ) when compared with the placebo group (86).

**Results:** The present study shows a reduction in diarrhea duration when *S. boulardii* was given to children within 72 hours after the onset of acute diarrhea.

**Conclusions:** The present study suggests a complementary treatment of acute diarrhea in infants with daily oral doses of *S. boulardii*.

**Key Words:** acute diarrhea, clinical trial, probiotic, rotavirus, *Saccharomyces boulardii*

(JPGN 2011;53: 497–501)

Acute gastroenteritis is the second most common life-threatening condition worldwide among all of the infectious diseases in children younger than 5 years, and the first cause of hospitalization (1). A variety of viral, bacterial, and parasitic organisms have been implicated in the pathogenesis of acute infectious diarrhea, and about 50% to 80% of episodes are caused by viruses, mainly rotaviruses and noroviruses. The management of acute diarrhea consists of the replacement of lost fluid with oral rehydration solution containing glucose and electrolytes; however, this solution

does not reduce the severity and the duration of diarrhea. The search for a treatment allowing such reduction started decades ago, and probiotics have been proposed as complementary therapy to the use of rehydration solution in the treatment of acute diarrhea (2).

According to the presently adopted definition by the Food and Agriculture Organization/World Health Organization, probiotics are “live microorganisms, which when administered in adequate amounts confer a health benefit to the host” (3). Several preparations containing different microorganisms have been tested in clinical trials and/or are commercially available. Meta-analyses of probiotic efficacy for acute diarrhea are available (4–7), and even though all of them concluded that probiotics have moderate clinical benefits in the treatment of acute diarrhea in children, they also considered that the results should be interpreted with caution because of the methodological limitations of the studies and that more research is needed. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition together with the European Society for Pediatric Infectious Diseases have concluded that probiotics may be used as an adjunct in the management of acute diarrhea and recommend 2 of them in particular, *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*, because of a higher volume of convincing data (8).

*S. boulardii* is a nonpathogenic yeast that has been used successfully for the prevention and/or the treatment of antibiotic-associated diarrhea, acute gastroenteritis in adults and children, and *Clostridium difficile*-associated disease (9,10). In the case of infectious diarrhea, administration of *S. boulardii* provides protection against intestinal lesions caused by several diarrheal pathogens (11). Five single- or double-blind controlled clinical trials using *S. boulardii* as a probiotic have been conducted for the treatment of acute diarrhea in children (12–16). Four among the 5 trials with the yeast showed it to be beneficial in children admitted to the hospital for diarrhea. In the fifth trial, which compared 5 different probiotic preparations, *S. boulardii* had no clinical effect. To explain these contradictory results, the authors of this last study suggest that the clinical conditions of the children could be responsible for the difference (more severe condition in almost all of the positive studies and mild to moderate diarrhea in the fifth trial).

There is a general consensus in the scientific literature that more clinical trials using probiotics are warranted because of numerous unanswered questions such as the efficiency of the treatment of infectious diarrhea depending on the etiologic agent. The present double-blind, placebo-controlled trial was performed to evaluate the efficacy of a commercial product containing *S. boulardii* for the treatment of acute diarrhea in hospitalized children.

## PATIENTS AND METHODS

### Trial Design

The trial was conducted using a double-blind, randomized, placebo-controlled, parallel-group design from April 2007 to

Received January 12, 2011; accepted June 20, 2011.

From the \*Departamento de Pediatria, Faculdade de Medicina, the †Departamento de Microbiologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, and the ‡Departamento de Pediatria e Puericultura, Universidade Federal de Goiás, Goiânia, Goiás, Brazil.

Address correspondence and reprint requests to Jacques R. Nicoli, PhD, Departamento de Microbiologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, 301270-901 Minas Gerais, Brazil (e-mail: jnicoli@icb.ufmg.br).

The study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento do Pessoal de Ensino Superior (CAPES).

The authors report no conflicts of interest.

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DOI: 10.1097/MPG.0b013e31822b7ab0

September 2008. The study was approved by the ethical council of the medical school, Universidade Federal de Goiás, and was registered as a clinical trial with the protocol number CEPMHA/HC/UFG 147/06. Before enrollment, the purpose of the study and the procedures were explained in detail, and written consent was obtained from the parents.

## Participants

Inclusion criteria were children of both sexes and ages 6 to 48 months, no other diarrhea episode or antibiotics use 2 weeks before the trial, and acute diarrhea within 72 hours before hospitalization. Exclusion criteria included exclusive breastfeeding, presence of macroscopic blood in the feces, severe malnutrition (weight/height <70% National Center for Health Statistics), impossibility of oral nutrition, existence of underlying pathology (eg, sepsis, cystic fibrosis, renal insufficiency, liver disease), and children needing specific treatment. The energy requirement for each infant was calculated and updated by a pediatric nutritionist who daily evaluated all of the patients admitted to the hospital. Parameters evaluated for eligibility of the patients were diarrhea duration before the intervention, dehydration state, number of evacuations 24 hours before the intervention, and stool consistency (liquid, semiliquid, soft, and formed). Diarrhea was defined as a change in bowel habits with a diminution of stool consistency and 3 or more evacuations per day with a duration of not more than 72 hours.

## Study Settings

Children hospitalized for acute diarrhea were screened at 1 of the 2 following hospitals: Hospital da Criança and Hospital Infantil de Campinas, both located in Goiânia, Goiás, Brazil.

## Interventions

*S. boulardii* was provided as capsules, which were purchased from a local pharmaceutical establishment (Floratil; Merck S.A., Rio de Janeiro, Brazil). The capsules contained 200 mg of the lyophilized yeast ( $4 \times 10^9$  viable cells) and magnesium stearate, lactose, and sucrose as excipients. Placebo capsules contained 200 mg of only the excipients and were prepared by the Faculdade de Farmácia, Universidade Federal de Goiás, Goiânia, Brazil. In the probiotic group, the patients were treated orally every 12 hours with the capsule containing the yeast for 5 days. In the control group, patients received placebo following the same schedule as the probiotic group.

## Outcomes

The endpoint was clinical cure of the diarrhea, which was considered to have occurred when evacuation frequency was <3 times per day or the stool consistency improved for at least 24 hours. During the trial period, if no improvement was observed in 4 days of intervention, then the therapy was discontinued and child was remanded for further treatment of diarrhea.

## Sample Size

The EpiInfo statistical package (version 6.04, Centers for Disease Control and Prevention, Atlanta, GA) was used to determine the sample size that would provide 80% power using a 2-sided test (with  $\alpha = 5\%$ ) for differences in proportions, based on an expected frequency of diarrhea with a duration higher than 3 days of 55% for the placebo group and 30% for the probiotic group.

Under these assumptions, the smallest sample size was 68 patients in each group, totaling 136 children. Taking into account a study withdrawal rate of 25%, the target sample size was increased to 170 patients.

## Randomization

The capsules were randomly coded by computer-generated numbers and distributed to the attending staff, which was composed of 2 physicians, 2 nurses, and 2 nutritionists.

## Blinding

Both placebo and lyophilized *S. boulardii* were packaged in identical capsules. Powders in both types of capsules were similar in texture and color, and the attending staff was unaware which product was being administered.

## Additional Analyses

The presence of rotavirus was detected in fecal samples from 162 patients using commercially available enzyme-linked immunosorbent assay kits (Oxoid, Basingstoke, UK).

## Statistical Methods

Data were analyzed using EpiInfo, and  $P < 0.05$  or  $P < 0.01$  were considered statistically significant depending on the data analyzed. Differences between group proportions were assessed using the Yates continuity-corrected  $\chi^2$  test. Analysis was performed both as per protocol and as intention to treat.

## RESULTS

Figure 1 shows that a total of 186 children with acute diarrhea fulfilled the protocol inclusion and exclusion criteria and were randomized in the probiotic (95) and placebo groups (91). In our trial, 3 patients from the probiotic group and 2 from the placebo group were excluded from analysis during the trial because of the need for antibiotic treatment, and 2 patients from the probiotic group and 3 from the placebo group were excluded because of withdrawal during the trial. By the end, 176 children completed the trial: 90 in the probiotic group and 86 in the placebo group. No adverse effects were noticed in the probiotic or placebo group that required discontinuation of the interventions.

Table 1 summarizes the subjects' baseline, demographic, and clinical characteristics. The 2 groups were comparable with regard to age, sex, and baseline features of acute diarrhea. Rotavirus also was detected in similar frequency in the 2 groups, with an average of 57.4% of the children with diarrhea tested for the presence of the virus.

Figure 2 shows that 2 days after the beginning of the intervention, the frequency of patients who remained with diarrhea was lower in the probiotic group when compared with the placebo group ( $P < 0.01$ ). The difference between the 2 groups was maintained by day 3 of intervention, with 32.2% of patients with diarrhea in the group treated with *S. boulardii* and 59.2% in the placebo group ( $P < 0.01$ ).

Intention to treat analysis (Table 2) shows that the frequency of patients with diarrhea 3 days after the beginning of treatment was lower in the group treated with *S. boulardii* when compared with the placebo group, which represents a statistically significant reduction in risk when the probiotic was used (relative risk [RR] 0.54, 95% confidence interval [CI] 0.38–0.66,  $P < 0.001$ ).

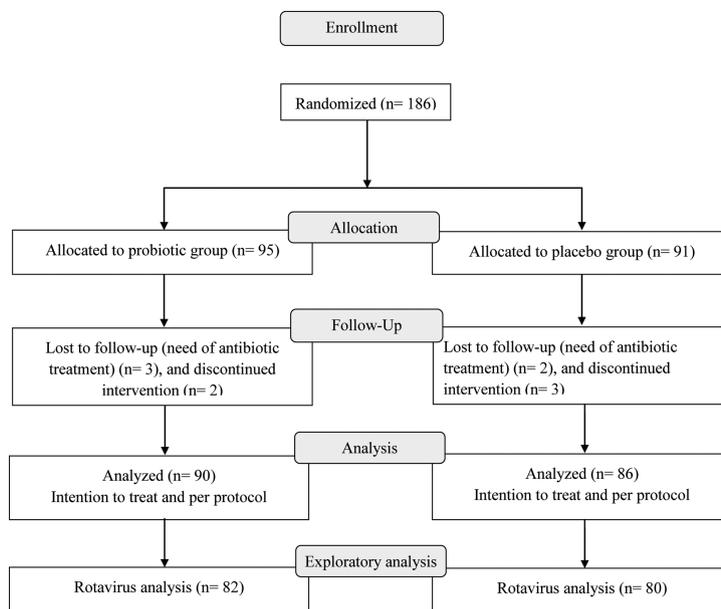


FIGURE 1. CONSORT diagram.

Per-protocol analysis showed similar results (RR 0.54, 95% CI 0.38–0.77,  $P < 0.001$ ).

Table 3 shows that in an exploratory analysis, when the children pertaining to the 2 types of intervention were separated into rotavirus-infected patients and nonrotavirus patients, the beneficial effect resulting from probiotic treatment was observed essentially for patients presenting with rotaviral diarrhea, with 29.2% of children who remained with diarrhea in the group treated with *S. boulardii* and 64.4% in the placebo group (RR 0.45, 95% CI 0.28–0.74). In patients with nonrotaviral diarrhea, 41.2% of children treated with *S. boulardii* remained with diarrhea, whereas in the placebo group, this frequency was 54.3% (RR 0.76, 95% CI 0.46–1.26); however, this difference was not confirmed as being significant when the ratio of the 2 relative risks tested as statistically different from 1 (ratio 0.60;  $P = 0.15$ ).

## DISCUSSION

Although oral rehydration solution remains the mainstay in the treatment of acute diarrhea, this therapy does not reduce the duration of diarrhea, prompting a growing interest in adjunctive treatments. The present study demonstrated that oral treatment with *S. boulardii* diminished in approximately 50% of the patients with

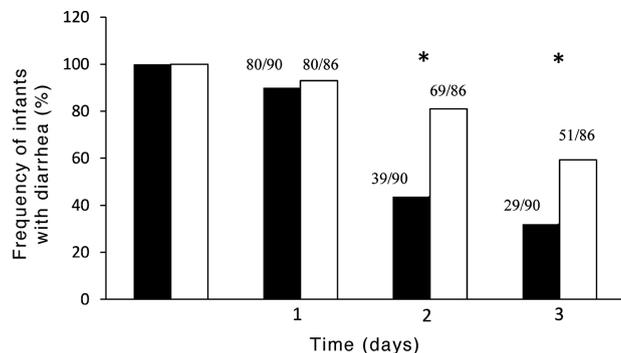
diarrhea since the second day after the beginning of the intervention when compared with a placebo group. The timing of the first administration of the probiotic appears to be critical, because the earlier the first administration of *S. boulardii*, the greater the efficacy. Vilarruel et al (14) showed that children given *S. boulardii* within 48 hours of the onset of diarrhea had significantly fewer number of stools than those who were administered the product when the duration of diarrhea was  $>48$  hours. This was the reason for the selection of patients with acute diarrhea within 72 hours before hospitalization as 1 of the inclusion criteria in the present study.

Diarrhea is a multifaceted disease with respect to etiology, and some intervention may be more or less effective with diarrhea caused by specific pathogens. To explore this possibility, the children were separated into 2 groups in each intervention type: rotavirus-infected patients and nonrotavirus patients. The mean frequency of patients with diarrhea caused by rotavirus in both intervention groups (57.4%) was slightly higher than the range from 16% to 52% that was observed in other studies in Latin America (17). The frequency of patients with diarrhea was lower in the rotaviral group (29.2%) than in the nonrotaviral group (41.2%), 3 days after the beginning of the intervention with the probiotic, but this difference was not found to be significant when the relative

TABLE 1. Baseline characteristics by study group

| Characteristics                                      | <i>S. boulardii</i> (n = 90) | Placebo (n = 86) |
|--|------------------------------|------------------|
| Age (mo $\pm$ SD)                                    | 23.0 $\pm$ 12.3              | 21.2 $\pm$ 11.8  |
| Sex (male/female)                                    | 47/43                        | 51/35            |
| Weight (kg $\pm$ SD)                                 | 10.6 $\pm$ 4.7               | 10.3 $\pm$ 4.5   |
| Height (cm $\pm$ SD)                                 | 83.6 $\pm$ 11.8              | 81.3 $\pm$ 12.4  |
| Diarrhea duration before intervention (h $\pm$ SD)   | 46.0 $\pm$ 13.5              | 50.2 $\pm$ 13.1  |
| No. evacuations 24 h before intervention ( $\pm$ SD) | 7.4 $\pm$ 3.8                | 7.9 $\pm$ 7.8    |
| No. infants with moderate to grave dehydration       | 88                           | 85               |
| Rotavirus detected, %                                | 58.5                         | 56.3             |

SD = standard deviation.



**FIGURE 2.** Frequency (%) of infants with diarrhea during the first 3 days after the beginning of the intervention with *S. boulardii* (■) and the placebo (□) as analyzed per protocol. \*Statistically different values ( $P < 0.01$ ).

risks in the 2 groups were compared statistically. Several controlled trials have shown that selected strains of lactobacilli (meanly *L. rhamnosus* GG) exhibited both therapeutic and prophylactic effects in children with viral but not bacterial diarrhea (18–20). In addition, *Bifidobacterium bifidum* combined with *Streptococcus thermophilus* has shown prophylactic activity against rotavirus gastroenteritis (21); however, an inverse result was obtained by Sarker et al (22) with *Lactobacillus paracasei* strain ST11, which had no effect on rotavirus but ameliorated the outcome of

nonrotaviral diarrhea in children from Bangladesh. To explain this discrepancy with the results obtained in the previous studies, the authors suggested that the difference could be related to the severity of the illness. In previously published studies, children were affected less severely than those in the study by Sarker et al (22). Curiously, this is the same argument used by Canani et al (15) to explain the lack of protective action of *S. boulardii* against acute diarrhea in children in their study when compared with 4 other clinical trials, but with an inverse finality. Interestingly, clinical evaluation and biological experiments in animal models showed that for *Lactobacillus* GG the protective effect against rotavirus was dependent on probiotic viability (23).

Concerning the mode of action of the probiotic, it is probable that >1 mechanism is involved when viruses are the pathogenic agents. Probiotics are well-known modulators of the mucosal immune response, stimulating its beneficial and/or suppressing deleterious aspects. Stimulation of the production of secretory immunoglobulin A and of reactive oxygen species ( $\text{NO}^-$  and  $\text{H}_2\text{O}_2$ ) by intestinal epithelial cells when treated with probiotic could explain a protective effect against virus (23–25). Secretory immunoglobulin A serves as the first line of defense against many mucosal pathogens, and in the case of rotavirus, protection against the infection appears to rely mainly on the production of neutralizing antibodies against the outer capsid proteins VP4 and VP7 (26). Another explanation could be the anti-inflammatory effect of *S. boulardii* resulting from yeast secretory protein(s), which inhibit(s) proinflammatory cytokines by interfering with the global mediator of inflammation nuclear factor- $\kappa\text{B}$  and modulating the activity of the mitogen-activated protein kinases

**TABLE 2.** Frequency of diarrhea 3 days after beginning of intervention with *S. boulardii* or placebo for patients, analyzed as per protocol and as intention to treat

| Analysis           | Groups (no. patients)    | Patients with diarrhea 3 d after beginning of intervention |           | P      | RR   | 95% CI    |
|--------------------|--------------------------|--|-----------|--------|------|-----------|
|                    |                          | Yes (%)  | No (%)    |        |      |           |
| Intention to treat | <i>S. boulardii</i> (95) | 29 (30.5)  | 66 (69.5) | 0.001  | 0.54 | 0.38–0.66 |
|                    | Placebo (91)             | 51 (56.0)  | 40 (44.0) |        |      |           |
| Per protocol       | <i>S. boulardii</i> (90) | 29 (32.3)  | 61 (67.8) | 0.0006 | 0.54 | 0.38–0.77 |
|                    | Placebo (86)             | 51 (59.2)  | 35 (40.8) |        |      |           |

CI = confidence interval; RR = relative risk.

**TABLE 3.** Frequency of diarrhea 3 days after beginning of intervention with *S. boulardii* or placebo for patients presenting or not rotavirus in groups in which presence of rotavirus was evaluated (n = 162)

| Groups (no. patients)   |                          | Patients with diarrhea 3 d after beginning of intervention |           | P      | RR   | 95% CI    | P, ratio RR, 95% CI |
|-------------------------|--------------------------|--|-----------|--------|------|-----------|---------------------|
|                         |                          | Yes (%)  | No (%)    |        |      |           |                     |
| Rotavirus positive (93) | <i>S. boulardii</i> (48) | 14 (29.2)  | 34 (70.8) | 0.0014 | 0.45 | 0.28–0.74 | 0.15                |
|                         | Placebo (45)             | 29 (64.4)  | 16 (35.6) |        |      |           |                     |
| Rotavirus negative (69) | <i>S. boulardii</i> (34) | 14 (41.2)  | 20 (58.8) | 0.395  | 0.76 | 0.46–1.26 | 0.30–1.20           |
|                         | Placebo (35)             | 19 (54.3)  | 16 (45.7) |        |      |           |                     |

CI = confidence interval; RR = relative risk.

ERK1/2 and p38 (27). Competition for attachment site onto epithelial intestinal cells between virus and probiotic could be another possibility as demonstrated in a vesicular stomatitis virus cell line infection (28). Complementary mechanisms of bacterium and yeast probiotic action are the trapping of pathogenic virus and bacteria by fixation onto its cell surface (28,29) and the production of metabolic compounds with antiviral activity as demonstrated for some lactic acid-producing bacteria against vesicular stomatitis virus (28). Finally, stimulation of the activity of brush border disaccharidases (lactase, sucrase) could be an additional mechanism to explain the antidiarrheal activity of the yeast (24).

Results from this clinical trial support the use of *S. boulardii* as an adjunctive treatment in acute diarrhea, based on a reduction of diarrhea duration when *S. boulardii* was given to children within 72 hours after the onset of acute diarrhea. The results also suggest a better apparent efficiency when rotavirus was the etiological agent, but this needs to be confirmed by larger specific follow-up studies.

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