

The Science Behind Diff-Stat® Ingredients

Saccharomyces boulardii

1. Surawicz CM, McFarland LV, Greenberg RN, et al. **The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*.** *Clin Infect Dis.* 2000;31:1012-1017.

In a double-blind, multicenter trial in 168 patients, *S. boulardii* plus a 10-day regimen of vancomycin 2 g/ day reduced the rate of recurrence of *C. difficile*-associated disease to 16.7%, versus 50% for the placebo group ($p = 0.05$). No serious adverse reactions resulted from the *S. boulardii* treatment. Comparison of data from this trial with data from previous studies indicates that recurrent CDD may respond to a short course of high-dose vancomycin or to longer courses of low-dose vancomycin when either is combined with *S. boulardii*.

2. McFarland LV, Surawicz CM, Greenberg RN, et al. **A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease.** *JAMA.*1994;271:1913-1918.

A double-blind, randomized, placebo-controlled, parallel-group intervention study in patients with active CDAD was conducted to determine the safety and efficacy of the combination treatment of *Saccharomyces boulardii* with an antibiotic (vancomycin hydrochloride or metronidazole). Patients received standard antibiotics and *S. boulardii* (1 g/d) or placebo for 4 weeks, and were followed up for an additional 4 weeks after therapy. A total of 124 eligible consenting adult patients, including 64 who were enrolled with an initial episode of CDAD, and 60 who had a history of at least one prior CDAD episode. The main outcome measure was recurrence of active CDAD. Patients treated with *S. boulardii* and standard antibiotics had a significantly lower relative risk (RR) of CDAD recurrence (RR, 0.43; 95% confidence interval, 0.20 to 0.97) compared with placebo and standard antibiotics. The efficacy of *S. boulardii* was significant (recurrence rate 35%, compared with 65% on placebo; in patients with recurrent CDAD).

3. Mehmet C et al. **Prophylactic *Saccharomyces Boulardii* in the prevention of antibiotic-associated diarrhea: a prospective study.** *Med Sci Monit.* 2006;12:119-122.

A double-blind controlled study investigated the preventive effect of *S. boulardii* on the development of AAD in 151 patients under antibiotic therapy. Subjects were patients that were hospitalized at the Gulhane Military Medical Academy, Department of Infectious Diseases and Clinical Microbiology. *S. boulardii* was given twice daily during the course of antibiotic therapy and application was initiated in all patients as late as after 48 hours of antibiotic therapy. Results showed a significant difference between the placebo 9% (7/78) and study group 1.4% (1/73) in the development of AAD. *C. diff* toxin A assay yielded positive results in two (2/7) stool samples from the patients with AAD in the placebo group and a negative result in the only patient who developed AAD in the study group. These results demonstrate that prophylactic use of *S. boulardii* results in reduced AAD, with no serious side effects, in hospitalized patients.

4. Surawicz CM, McFarland LV, Elmer G, Chinn J. **Treatment of recurrent *Clostridium difficile* colitis with vancomycin and *Saccharomyces boulardii*.** *Am J Gastroenterol.* 1989;84:1285-1287.

A clinical trial was conducted to evaluate the efficacy of *S. boulardii* in treating recurrences of *C. difficile*-associated colitis in humans. Thirteen patients with recurring *C. difficile* cytotoxin-positive diarrhea (who had an average of 3.6 previous recurrences) were treated with 10 days of vancomycin and a 30-day course of *S. boulardii*. Results showed that eleven (85%) had no further recurrences.

5. McFarland LV et al. **Prevention of β -Lactam associated diarrhea by *Saccharomyces Boulardii* compared with placebo.** *Am J Gastroenterol.* 1995; 90: 3: 439-448.

A double-blinded, placebo-controlled, parallel group study was performed in a high-risk group of hospitalized patients receiving a new prescription for a beta-lactam antibiotic to determine the safety and efficacy of adjunct treatment with *S. boulardii* for the prevention of AAD. *S. boulardii* or placebo (1 g/day) was given within 72 h of the start of the antibiotic(s) and continued until 3 days after the antibiotic was discontinued, after which the patients were followed for 7 weeks. Of the 193 eligible patients, significantly fewer, 7/97 (7.2%), patients receiving *S. boulardii* developed AAD compared with 14/96 (14.6%) on placebo. The efficacy of *S. boulardii* for the prevention of AAD was 51%. Using a multivariate model to adjust for two independent risk factors for AAD (age and days of antibiotic use), the adjusted relative risk was significantly protective for *S. boulardii*. The authors concluded that the prophylactic use of *S. boulardii* given with a beta-lactam antibiotic resulted in a significant reduction of AAD with no serious adverse reactions.

6. Surawicz CM, Elmer GW, Speelman P, McFarland LV, Chinn J, van Belle G. **Prevention of antibiotic-associated diarrhea by *Sacchomyces boulardii*: a prospective study.** *Gastroenterology.* 1989;96:981-988.

A prospective double-blind controlled study was performed in 180 hospitalized patients to evaluate the effect of *S. boulardii*, given in capsule form concurrently with antibiotics on the prevention of AAD over a 23 month period. Of the patients receiving placebo, 22% experienced diarrhea compared with 9.5% of patients receiving *S. Boulardii* which was significantly different. Risk factors found to be associated with AAD were multiple antibiotic combinations and tube feeding. Of *C. difficile*-positive patients, 31% (5/16) on placebo developed diarrhea compared with 9.4% (3/32) on *S. boulardii*. There were no discernable adverse effects of *S. boulardii* administration. The authors conclude that *S. boulardii* reduces the incidence of AAD in hospitalized patients.

7. McFarland LV. **Meta-analysis of probiotics for the prevention of Antibiotic Associated Diarrhea (AAD) and the treatment of *Clostridium difficile* disease.** *Am J Gastroenterol.* 2006; 101; 1-11.

This meta-analysis compared the efficacy of probiotics for the prevention of AAD and the treatment of CDAD based on the published randomized, controlled clinical trials. Data was obtained from PubMed, Medline, Google Scholar, NIH registry of clinical trials, metaRegister, and Cochrane Central Register of Controlled Trials from 1977 to 2005, unrestricted by language. Trials were required to be randomized, controlled, blinded efficacy trials in humans published in peer-reviewed journals in which probiotics were given to prevent or treat AAD and CDAD. Thirty-one of 180 screened studies (totally 3,164 subjects) met the inclusion and exclusion criteria. From 25 randomized controlled trials, probiotics significantly reduced the relative risk of AAD (RR = 0.43, 95% CI 0.31, 0.58, $p < 0.001$). From six randomized trials, probiotics had significant efficacy for CDAD (RR = 0.59, 95% CI 0.41, 0.85, $p = 0.005$). Using meta-analyses, three types of probiotics (*Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG, and probiotic mixtures) significantly reduced the development of AAD but only *S. boulardii* was effective for CDAD.

8. Szajewska H, Mrukowicz J. **Meta-analysis: non-pathogenic yeast *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea.** *Pharmacol Ther*, 2005; 22(5): 365-72.

A meta-analysis was conducted to systematically evaluate the effectiveness of *S. boulardii* in preventing AAD in children and adults. Using medical subject headings and free-language terms, the following electronic databases were searched for studies relevant to AAD and *S. boulardii*: MEDLINE, EMBASE, CINAHL and The Cochrane Library. Additional sources were obtained from references in reviewed articles. Only randomized-controlled trials were considered for study inclusion. Of 16 potentially relevant clinical trials identified, five randomized-controlled trials (1076 participants) met the inclusion criteria for this systematic review. Treatment with *S. boulardii* compared with placebo reduced the risk of AAD from 17.2% to 6.7%. A meta-analysis of data from five randomized-controlled trials showed that *S. boulardii* is effective in preventing AAD in children and adults treated with antibiotics for any reason.

9. L. V. McFarland, P. Bernasconi. ***Saccharomyces boulardii*: A Review of an Innovative Biotherapeutic Agent.** *Microbial Ecology in Health and Disease* 1993 Vol. 6:157-171.

Saccharomyces boulardii is a non-pathogenic yeast which has been used as both a preventive and therapeutic agent for the treatment of a variety of diarrheal diseases. The studies with animal models and evidence from human volunteers and patients indicate a profile which is effective in the therapy of diarrhea and is remarkably safe for oral ingestion. The pharmacokinetic data demonstrate that *S. boulardii* reaches a steady-state concentration quickly and maintains a high stable level as long as the yeast is taken daily. Once the agent is discontinued, *S. boulardii* is quickly eliminated from the colon. Clinical trials studying AAD, nasogastric-tube alimentation diarrhea, *Clostridium difficile*-disease, acute diarrhea and chronic diarrhea in HI V-infected patients are reviewed in this article.

Bacillus coagulans (Lactobacillus sporogenes) and FOS

10. LaRosa M, Bottaro G., Gulino N, et. Al. **Prevention of antibiotic-associated diarrhea with *Lactobacillus sporogenes* and fructo-oligosaccharides in children.** A multicentric double-blind vs placebo study. *Minerva Pediatr.* 2003 Oct; 55(5):447-52.

A multicentre, randomized, double-blind placebo controlled study was conducted to determine the efficacy of a fructo-oligosaccharides (FOS) combine with *Lactobacillus sporogenes* supplement in the prevention of AAD in children. A total of 120 children, with active infections requiring antibiotics, were enrolled in the study and treated for 10 days either in the experimental group (F) or in the placebo one (P). The results of the study were recorded from the patients' diary and from follow-up clinical examinations. Out of 98 evaluable patients, 71% in group F had no diarrhea versus 38% in group P. There was a significant difference in the duration of diarrhea in F and P groups, 0.7 vs 1.6 days, respectively. The authors concluded that prophylaxis with *Lactobacillus sporogens* combine with FOS, significantly reduced the number of days and duration of events in children with AAD.

Gibson GR et al. **Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin.** *Gastroenterol* 1995;108:975–82.

This study showed that Fructooligosaccharides (FOS) are fermented predominantly by bifidobacteria (beneficial bacteria) and consumption of FOS in adults resulted in a significant numerical predominance of bifidobacteria in the colon.