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Saccharomyces boulardii as a Probiotic for Children

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S *accharomyces boulardii* (*S. boulardii*) has been used as a probiotic agent since the 1950s. It has been shown to be useful in the treatment of acute infectious diarrhea, the prevention or treatment of diarrhea associated with antibiotic use, and as an adjunctive therapy for *Helicobacter pylori* infection. It has also been suggested as a formula supplement for premature infants.¹⁻⁴ This issue of *Pediatric Pharmacotherapy* will describe the studies published to date on *S. boulardii* in infants and children and provide an overview of the adverse effects and dosing recommendations for this agent in infants, children, and adults.

Mechanism of Action

Probiotics are live non-pathogenic microorganisms that are taken orally to aid in the maintenance and/or restoration of healthy gastrointestinal (GI) microflora. In addition to *S. boulardii*, other probiotics include *Lactobacillus rhamnosus* strain GG (formerly *L. casei* GG), *L. reuteri*, *L. acidophilus*, *Bifidobacterium* spp., and *Streptococcus* spp. preparations.^{1,2} While most probiotics are bacteria, *S. boulardii* is a non-colonizing, non-systemic yeast. It was first isolated in 1923 from lychee fruit in Indonesia by French scientist Henri Boulard who noted that natives of the area used the skin of the fruit to treat symptoms of cholera.^{2,5,6}

While the mechanisms by which probiotics exert their benefit are not fully understood, it has been suggested that they improve host barrier function, produce competitive inhibition of pathogenic bacteria, and bolster immune function. *S. boulardii* secretes enzymatic proteins, including a protease that degrades *Clostridium difficile* toxins and a phosphatase that inactivates endotoxins such as the lipopolysaccharide produced by *E. coli*. It also strengthens tight junctions between enterocytes (reducing chloride secretion), promotes maturation of the intestinal brush border membrane and stimulates production of glycoproteins (including secretory IgA). *S. boulardii* also promotes production of disaccharidases such as lactase, sucrase, maltase, and N-aminopeptidase in the brush border

allowing increased carbohydrate degradation and absorption in patients with diarrhea, and restores normal levels of short chain fatty acids in the colon which are necessary for absorption of water and electrolytes. In addition, *S. boulardii* may reduce inflammation in the GI tract by stimulating regulatory T cells and inhibiting mitogen-activating protein (MAP) kinase and nuclear factor-kappa B (NF- κ B) signal transduction pathways, resulting in decreased secretion of interleukin (IL-8) and tumor necrosis factor alpha (TNF α). *S. boulardii* also decreases inducible nitric oxide synthase (NOS) activity and up-regulates proliferator-activated receptor-gamma (PPAR- γ), leading to a reduction in intestinal inflammation.¹⁻⁴

Pharmacokinetics and Pharmacodynamics

Daily administration of lyophilized *S. boulardii* at standard doses results in detectable levels of live yeast throughout the GI tract. *S. boulardii* does not attach to the mucosa of the intestine. A stable concentration is reached within 3 days in adults. A week after discontinuing treatment, *S. boulardii* can no longer be detected in the bowel lumen. Several investigators have documented a correlation between the concentration of the yeast in GI tract and the degree of symptomatic improvement following *C. difficile* infection in both animal models and clinical trials.³

Clinical Trials in Infants and Children

Treatment of Acute Infectious Diarrhea

Since the mid-1980s, several case series, open prospective studies, and randomized controlled trials have evaluated the efficacy of *S. boulardii* in the treatment of acute diarrhea associated with gastroenteritis in children. In 2007, Szajewska and colleagues conducted a meta-analysis of the results from five studies comparing *S. boulardii* to placebo or no intervention.⁷ A total of 619 children were enrolled in these trials, with *S. boulardii* doses of 250 to 600 mg/day or placebo given for 4 to 6 days. Four studies included the duration of diarrhea as an outcome, with all demonstrating a significant reduction with treatment. The combined data from these

studies provided a pooled weighted mean difference of -1.1 days (95% CI: -1.3 to -0.8). Single studies used in this analysis also documented a reduction in the risk of diarrhea lasting more than 7 days, as well as a reduction in length of hospital stay. The authors concluded that treatment with *S. boulardii* had a moderate clinical benefit in the treatment of acute diarrhea in otherwise healthy children.

An additional randomized controlled trial was published by Htwe and colleagues in 2008.⁸ The authors enrolled 100 Myanmar children between 3 months and 10 years of age with acute diarrhea. The children received oral rehydration solution with or without *S. boulardii* 250 mg given twice daily for a period of 5 days. The mean duration of diarrhea was 3.08 days in the *S. boulardii* group compared to 4.68 days in the controls ($p < 0.05$). On the second day, 27 (54%) of the treatment group were having less than 3 stools per day, compared to only 15 (30%) of the controls ($p = 0.19$). Stool consistency was no different between the groups on day 2; however by day 3, stool consistency has returned to normal in 38 (76%) of the treatment group versus 12 (24%) of the controls ($p = 0.019$). The authors concluded that treatment resulted in a shortened duration of acute diarrhea, which could produce significant societal and economic benefits.

Treatment of Chronic Diarrhea

In addition to the treatment of acute diarrhea, *S. boulardii* has also been found to be beneficial in children with chronic diarrhea. Castaneda Guillot and colleagues conducted a randomized, double-blind, placebo-controlled trial in 40 infants and children (ages 6 to 36 months) with chronic diarrhea.⁹ The study patients included 35 children with *Giardia lamblia*, 4 with *Shigella*, and one patient with chronic diarrhea of an undetermined etiology. The 39 patients with known infections had undergone standard treatment with an appropriate antimicrobial or antiparasitic. The patients were randomized to receive either *S. boulardii* 250 mg or placebo orally twice daily for one month. Prior to initiation of the study, the average number of stools was 4-6 per day. At the end of the study, 65% of the patients in the *S. boulardii* group were having normal stool frequency, defined as 1-3 stools/day, compared to only 15% of the controls ($p = 0.006$). Histologic improvement was also found in the *S. boulardii* group; the number of patients with normal jejunal mucosa increased from 15% at baseline to 35% by the end of the study. In comparison, there was no change in the controls. There were no adverse events reported.

Persistent *C. difficile* infection has also been found to improve with *S. boulardii* therapy.¹⁰ Buts and colleagues treated 19 infants (average age 8 months) with persistent intestinal symptoms related to *C. difficile* overgrowth. The patients were treated with *S. boulardii* 250 mg given two to four times per day for 15 days. Within 1 week of starting therapy, 95% had improvement in symptoms with a significant reduction in stool frequency ($p < 0.001$). In 85% of the cases, toxin B was cleared by the end of treatment, while eradication of *C. difficile* was complete in 14 patients (73%) by one month. Two patients relapsed after the end of treatment, but responded to a second 15-day course. Additional research, with larger sample sizes, is needed to substantiate these early studies.

Prevention of Antibiotic-associated Diarrhea

Two randomized controlled studies have found a beneficial effect of *S. boulardii* in the prevention of antibiotic-associated diarrhea, including that caused by *C. difficile*.^{11,12} In 2004, Erdevé and colleagues enrolled 653 children between 1 and 15 years of age in a study evaluating the efficacy of *S. boulardii* during treatment with ampicillin/sulbactam or azithromycin.¹¹ Four hundred sixty-six children completed the study. Antibiotic-associated diarrhea was observed in 14 (5.7%) of the 244 children given *S. boulardii* during their antibiotic course, compared to 42 (19%) of the 222 controls ($p < 0.05$). When separated by drug, the effect of *S. boulardii* was statistically significant only for the ampicillin/sulbactam group (5.9% incidence in the treatment group compared to 25.6% in the controls, $p < 0.05$) and was most pronounced in children less than 6 years of age.

The following year, Kotowska and colleagues published a second randomized controlled trial with *S. boulardii* in 269 children (6 months to 14 years of age).¹² All of the children were treated with antibiotics after diagnosis of otitis media or a respiratory tract infection. The most frequently used antibiotics in the study were amoxicillin, cefuroxime, clarithromycin, penicillin, and roxithromycin. The patients were randomized to receive either *S. boulardii* 250 mg or placebo twice daily for the duration of antibiotic therapy. The incidence of antibiotic-associated diarrhea (including *C. difficile* diarrhea) in the treatment group was only 3.4% compared to 17.3% in the controls (RR 0.2, 95% CI: 0.07-0.5). None of the patients required discontinuation of antibiotics or hospitalization, and no adverse events were reported. The results of these two studies are similar to a number of clinical trials in adults demonstrating the utility of *S. boulardii* in preventing antibiotic-associated diarrhea.

Use in *H. pylori* Infection

Probiotics, including *S. boulardii*, have been used in several clinical trials in children and adults to improve the efficacy and/or tolerability of eradication therapy in patients with *H. pylori* infection. In 2005, Gotteland and colleagues compared the effects of *Lactobacillus acidophilus* or *S. boulardii* plus inulin on *H. pylori* colonization in children.¹³ A total of 254 children who tested positive for *H. pylori* were randomly assigned to receive either antibiotic treatment consisting of lansoprazole, clarithromycin, and amoxicillin for 8 days or one of the two probiotics for 2 months. *H. pylori* eradication was achieved in 66% of the children receiving antibiotics, 12% of those given *S. boulardii* plus inulin, and 6.5% of those given *Lactobacillus*. Based on their results, the authors proposed that *S. boulardii* with inulin may be a useful option to interfere with *H. pylori* colonization in asymptomatic children not requiring eradication therapy or in those unable to be treated with antibiotics.

Earlier this year, Hurduc and colleagues published the results of their randomized placebo-controlled open trial of *S. boulardii* in 90 symptomatic children with *H. pylori* infection.¹⁴ All children received triple therapy with omeprazole/esomeprazole, clarithromycin, and amoxicillin for 7 to 10 days and were randomized to receive either *S. boulardii* 250 mg or placebo twice daily for 4 weeks. The *H. pylori* eradication rate was not significantly different between the groups (93.3% in the *S. boulardii* group versus 80.9% in the controls), but the incidence of adverse effects associated with triple therapy was significantly lower in the *S. boulardii* group compared to the controls (8.3% versus 30.9%, $p=0.047$).

Enteral Feeding Supplementation

Only one study to date has evaluated the prophylactic use of *S. boulardii* in premature infants. In 2003, Costalos and colleagues randomized 87 healthy infants between 28 and 32 weeks gestational age to receive a preterm formula with either *S. boulardii* or maltodextrins added for 30 days.¹⁵ At the end of the study, the mean log of colony-forming units/gram stool for *E. coli* and enterococci was significantly lower in the *S. boulardii* group ($p<0.05$), while the number of beneficial bifidobacteria and staphylococci in the stools was significantly higher ($p<0.001$). There were no differences in weight gain or absorption of D-xylose or lipids between the groups. The authors concluded that *S. boulardii* supplementation brought stool flora closer to the pattern of breast fed babies, but did not improve nutrient absorption.

Adverse Effects

Probiotics are generally well tolerated. The most significant risk associated with their use has been systemic infection. Epidemiologic studies have suggested a low rate of infection, ranging from 0.05 to 0.4%. While *S. boulardii* has been successfully used by thousands of people, health care providers should be aware that over 30 cases of systemic fungal infection have been associated with its use. Beginning with the initial reports in 1995, ten cases of fungemia have been reported in children, including five infants. Treatment with an antifungal (amphotericin or fluconazole) was usually effective in eradicating the infection.^{2,16} In two more recent case reports, voriconazole was used successfully after fluconazole treatment failure.^{17,18}

Risk factors for systemic infection include long-term hospitalization, treatment with antibiotics, severely immunocompromised states or use of immunosuppressive agents, and the presence of exogenous materials such as prosthetic heart valves, shunts, or catheters. The use of central venous catheters appears to be one of the most significant factors predisposing patients to systemic infection. Airborne yeast from open capsules or powder packets can be deposited onto the catheter hub or port, allowing contamination when the catheter is accessed.^{2,16}

In their series of four cases, Hennequin and colleagues reported that nearby surfaces remained contaminated with *S. boulardii* up to 30 minutes after opening a packet.¹⁹ In the hospital setting, it is recommended that packets be opened in an area other than patients' rooms and by a health care provider wearing gloves. Administration of *S. boulardii* in patients with central venous catheters, particularly those who are immunocompromised, should be undertaken only after a full analysis of the potential risk.²

Unlike *Lactobacillus* spp., *S. boulardii* has not been associated with infections resulting from translocation from the gastrointestinal tract into the systemic circulation. However, as a safeguard, most clinicians avoid use of all probiotics in patients with known or potential compromise of gut integrity.^{2,3}

Drug Interactions

Azole antifungals, including fluconazole and itraconazole, may inactivate *S. boulardii* organisms. Although this interaction has not been well studied, it has been recommended that *S. boulardii* be administered at least 1 hour before or 2 hours after an antifungal dose.²⁰

Dosing Recommendations

S. boulardii is most commonly marketed in a lyophilized freeze-dried form (*S. boulardii* Iyo). The recommended dose of *S. boulardii* in children over 2 months of age is 250 mg given twice daily. Although the product is available without a prescription, it is recommended that it not be used in children under 2 years of age without the supervision of a health care provider. The usual adult dose is 500 mg (2 capsules) once daily for the prevention of diarrhea or twice daily for treatment. Treatment duration typically ranges from 1 to 4 weeks for acute or antibiotic-associated diarrhea.^{1-4,6,20}

S. boulardii may be used in combination with other probiotics. It may be administered with or without food. The powder should be mixed with water, milk, or juice and swallowed immediately after mixing. Storage conditions differ by manufacturer.^{6,20}

Availability and Cost

Lyophilized *S. boulardii* is available from a wide number of manufacturers. One of the more widely used brands is Florastor® (Biocodex, Inc.), which is available as 250 mg capsules and tutti-fruitti flavored oral powder packets for children (Florastor® KIDS). The suggested retail price for a bottle of 10 capsules is \$10.95 and a bottle of 50 capsules is \$43.95. A box of 10 powder packets is priced at \$12.95.^{6,21}

Summary

Over the past decade, there has been a significant increase in the number of studies demonstrating the utility of probiotics in children and adults with diarrhea or related conditions. *S. boulardii*, a yeast isolated more than half a century ago, has more clinical trial data than most other agents in this class. While several studies support its use in children, additional research is needed on the long-term implications of treatment and the risk for systemic infection.

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Formulary Update

The next Pharmacy and Therapeutics Committee meeting will be held on 7/24/09.

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