Saccharomyces boulardii

Introduction

Saccharomyces boulardii, a nonpathogenic yeast, is a subspecies of *Saccharomyces cervisiae* (Brewer's yeast) and has a similar structure. *S. boulardii* has been shown to be effective in the treatment of antibiotic-associated diarrhea, recurrent *Clostridium difficile*-associated disease, Crohn's Disease, and HIV/AIDS-associated diarrhea.

Pharmacokinetics

Subsequent to oral administration and transport to the gastrointestinal tract, *S. boulardii* cells undergo irreversible degradation. In the large intestine, live cells are exposed to saccharolytic enzymes produced by the normal intestinal flora that hydrolyze polysaccharides in the cell wall. These same enzymes act to further degrade dead cells as well. Ultimately, *S. boulardii* appears in the bowel and feces.[1,2] Research indicates *S. boulardii* does not appear to colonize the intestinal tract, and a single oral dose is rapidly eliminated in the feces.[2] When *S. boulardii* was monitored in stools of patients given a dose of one gram daily, only one percent of the ingested dose was present and the organism was cleared completely from the stool within three days.[2] Conversely, when *S. boulardii* is administered to animals continuously (in drinking water), the fecal concentration of live cells is increased 50-100-fold, suggesting frequent dosing may be more effective.[3] In studies of patients taking ampicillin, *S. boulardii* recovery in the stool was increased 2.4 times, indicating when normal intestinal flora is altered, the level of *S. boulardii* in the intestine is elevated.[4]

Mechanisms of Action

S. boulardii appears to be taken up by the intestinal villa and to adhere to cells in the jejunum,[5,6] increasing brush border enzyme activity of lactase, alpha-glucosidase, and alkaline phosphatase, and increasing normal enterocyte maturation.[7] *S. boulardii* also exerts a protective effect on epithelial cells infected with *E. coli* by decreasing the level of intracellular infection and reducing the apoptotic effect of *E. coli* on intestinal epithelium.[8] *S. boulardii* has also been shown to increase intestinal secretory IgA production[9] and, in one human study, to activate the reticuloendothelial system, probably via a non-specific response.[10] In addition, *S. boulardii* neutralizes toxins produced by *Vibrio cholera* in epithelial cells of rat jejunum,[11]

and prevents *Entamoeba histolytica* from adhering to human erythrocytes, a model of the first step in amoebic infection in humans.[12]

In *C. difficile*-related diarrhea and pseudomembranous colitis, Clostridium toxins bind to membrane receptors, causing intestinal fluid secretion and increased permeability of intestinal mucosa. *S. boulardii* contains a protease that neutralizes *C. difficile* toxins A and B, and also digests membrane receptors that bind to *C. difficile* toxin in the brush border epithelium of the ileum, thus exerting a protective effect on the gut lining.[13]

Clinical Indications

Antibiotic-associated Diarrhea

Antibiotic-associated diarrhea (AAD) occurs in 5-25 percent of patients receiving antibiotic therapy, and in cases of nosocomial epidemics the incidence has reached as high as 29 percent in hospitalized populations.[14] AAD is due primarily to infection with *Clostridium difficile* (20% of all cases) and less frequently to *Klebsiella oxytoca, Clostridium perfringens, Staphylococcus aureus, Candida sp., and Salmonella sp*.[15] The total incidence of gut-related disease caused by *C. difficile* ranges from 5-21 percent in hospitalized patients.[16,17] *C. difficile* diarrhea may manifest anywhere on the spectrum of AAD, acutely or 2-6 weeks post-antibiotic cessation. Twenty percent of patients with *C. difficile* diarrhea acquire pseudomembranous colitis, and fatality rates for recurrent pseudomembranous colitis may be as high as 10 percent in some populations.[14] After treatment with vancomycin or metronidazole, 20 percent of patients with *C. difficile*-associated diarrhea will continue to have diarrhea or colitis after medications are discontinued. Continued antibiotic treatment usually worsens the situation, resulting in prolonged symptomology.[16] Because *S. boulardii* is resistant to most antibiotics, it can be given simultaneously to prevent antibiotic-associated diarrhea.[18]

Studies of *S. boulardii* during and beyond the course of antibiotics in *C. difficile* diarrhea have shown it to be effective in preventing the return of *C. difficile,* as well as eliminating symptoms of infection.[19-22]

In one such case, the persistent nature of *C. difficile* infection is presented. Over an eight-month period, a patient with six documented cases of recurrent *C. difficile* colitis experienced repeated relapses, despite antibiotic treatment with four different antibiotics. Four episodes required hospitalization and rehydration.[19] Initial stool cultures showed high titers of *C. difficile* toxin that dropped rapidly during treatment with *S. boulardii* at a dosage of one gram daily for 28 days. Within seven days of *S. boulardii* administration the *C. difficile* toxin titer was zero. Diarrhea went into remission during the treatment period and on follow-up 18 months later, no further symptoms had occurred.[19]

Studies with documented recurrent *C. difficile* infection treated by standard antibiotic therapy along with *S. boulardii* have shown significant decreases in recurrence rates.[20-22] One double-blind, randomized, eight-week trial of 124 patients involved standard antibiotic therapy

(metronidazole or vancomycin) for an average of 16 days in addition to *S. boulardii* one gram daily for 28 days (with overlap of antibiotic and *S. boulardii* for eight days).[20] Individuals who had a history of recurrent *C. difficile* infections were given high-dose vancomycin (two grams daily) and *S. boulardii,* and had a recurrence rate of zero. Those on vancomycin and placebo had a recurrence rate of 50 percent. Patients on low-dose vancomycin and *S. boulardii* had a 21 percent recurrence rate, compared to a rate of 62 percent recurrence with low-dose vancomycin and placebo. Even when all patients in the study (regardless of antibiotic type) with recurrent *C. difficile* were taken into account, the addition of *S. boulardii* significantly decreased the risk of recurrence (34.6% vs. 64.7% on placebo). There was, however, no beneficial effect of *S. boulardii* administration for those experiencing an initial episode of *C. difficile*-related diarrhea.[20] In a follow-up study using only high-dose vancomycin for 10 days and *S. boulardii* for 28 days (with an overlap of four days), 16.7 percent of patients on *S. boulardii* treatment had a repeated infection, while 50 percent on vancomycin and placebo had a recurrence.[21]

S. boulardii has also been used in infants and children with *C. difficile* enteropathies.[22] In 19 children (median age eight months), all of whom received a course of antibiotics for at least three days prior to enrollment, symptoms of diarrhea, malabsorption, or failure to thrive occurred as a result of *C. difficile* infection. The children were given *S. boulardii* in the following age-adjusted doses: 250 mg twice daily for those younger than one year; three times daily for those one to four years of age; and four times daily for those older than four years of age. The dosing regimens were continued for 15 days. In all but one child, symptoms resolved within seven days of treatment. Clearing of *C. difficile* toxin B occurred in 85 percent of the children after 15 days and in 73 percent of the children 30 days after treatment began. Most significantly, two months after initiation of treatment the pathologic changes (sparse and shortened microvilli) that had occurred in the colons of those most affected returned to normal on biopsy sampling. Two patients who experienced relapses were retreated with a two-week trial of *S. boulardii* and responded within seven days without further recurrences.[22]

In three placebo-controlled studies of AAD in adults (without benefit of stool cultures), *S. boulardii* was given in doses of one gram daily for 14 days. Treatment resulted in significant symptom reduction compared to placebo in all three studies. Those left unimproved on *S. boulardii* versus unimproved on placebo were: 9.5 percent versus 22 percent,[23] 7.2 percent versus 14.6 percent,[24] and 4.5 percent versus 17.5 percent.[25]

Irritable Bowel Syndrome

In a controlled trial of 34 patients with prior diagnosis of irritable bowel syndrome, the administration of *S. boulardii* was effective in decreasing diarrhea but did not affect abdominal pain and bloating.[26]

Crohn's Disease

In a placebo-controlled trial, 20 patients with established Crohn's disease and chronic diarrhea were given 250 mg *S. boulardii* three times daily for two weeks in addition to the basic treatment.[27] A significant reduction in frequency of bowel movements occurred, along with a reduction of scores in an index of disease activity (BEST index) when compared to baseline. At the end of two weeks, seven patients were placed in the control group and received placebo for an additional seven weeks. Ten of the 20 patients remained in the treatment group and continued to receive *S. boulardii*, 250 mg three times daily for seven weeks. The treatment group continued to show a significant reduction in bowel movement frequency and BEST index scores. Conversely, the placebo group had an increase in bowel movement frequency, and BEST index scores rose again until reaching initial values in the tenth week.[27]

In another trial, 32 patients with stabilized Crohn's disease were treated with either mesalamine or mesalamine and *S. boulardii* (one gram daily). After six months, 37.5 percent of the patients on mesalamine alone experienced relapse, while only 6.25 percent of patients on both therapies relapsed.[28]

HIV/AIDS

Although studies of *S. boulardii* in HIV patients have been limited, they are noteworthy. Three small trials were conducted in HIV-positive and AIDS-diagnosed individuals with diarrhea of unknown etiology. In one trial utilizing three grams daily of *S. boulardii*, fecal stool weights decreased significantly and stools became fully formed.[29] In another small trial, stool frequency decreased from nine to two stools per day and average body weight gain was 17.7 pounds.[30] In a placebo-controlled trial with 36 AIDS patients in which antibiotic treatment had been unsuccessful, 55 percent of patients given *S. boulardii* became diarrhea-free and only six percent of the placebo group regained normal stool function.[31]

Side Effects and Toxicity

While few side effects have been reported, Saccharomyces fungemia has been documented in immunosuppressed infants,[32] in hospitalized infants on *S. boulardii* therapy,[33] and in patients with in-dwelling vascular catheters.[34] Ingestion of therapeutic dosages of *S. boulardii* may cause flatulence.

Dosage

In most of the literature *S. boulardii* dosages are expressed in mg or gram amounts per day. However, the number of live organisms per gram is not listed in most literature. Clinically, it appears 10-20 billion organisms per day is an effective adult dosage range. Because *S. boulardii* is resistant to most antibiotics, it can be given simultaneously to prevent antibiotic-associated diarrhea.[18]

Warnings and Contraindications

Individuals with a yeast allergy should avoid *Saccharomyces boulardii* as it may cause itching, rash, and other common allergic symptoms. Immunosuppressed individuals should use *S. boulardii* with caution.

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