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Treatment of Recurrent *Clostridium difficile* Colitis with Vancomycin and *Saccharomyces boulardii*

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Recurrence of *Clostridium difficile*-associated diarrhea and pseudomembranous colitis occurs in up to 20% of patients after standard therapy. In these patients, subsequent recurrences are even more frequent. *Saccharomyces boulardii*, a nonpathogenic yeast, was found to be effective in preventing clindamycin cecitis recurrence in an animal model. We performed an open trial of *S. boulardii* to evaluate its efficacy 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.* Eleven (85%) had no further recurrences. *S. boulardii* may have a role in treating recurrent *C. difficile* diarrhea and colitis.

INTRODUCTION

Although *Clostridium difficile*-associated diarrhea and pseudomembranous colitis (PMC) can be effective1y treated with vancomycin, metronidazole, or bactracin, 20% of patients suffer recurrence after treatment (1-7). After one recurrence, additional recurrences are even more likely-up to 63% have subsequent recurrences (4, 5). Diarrheal recurrence may be due to persistent *C. difficile* spores which are resistant to antibiotic therapy. Standard therapy consist of metronidazole, pulsed or long tapering courses of vancomycin, or vancomycin followed by the toxin-binding resin, cholestyramine (4). An attractive approach to decreasing the recurrence rate is the addition of microorganisms to the gastrointestinal tract that would restore homeostasis, and several investigators have explored this possibility. Although esthetically unappealing, rectal infusions of normal feces have been used with success in several intractable cases of colitis (8, 9). In addition, five patients with recurring *C. difficile* colitis had resolution of symptoms after the administration of a specific strain of *Lactobacillus* (10).

Saccharomyces boulardii is a nonpathogenic yeast, not currently commercially available in the United States, with an unusual optimum growth temperature of 37°C.

This yeast was originally isolated growing on lychee fruit in Indochina in the 1920s and, since 1962, has been used in Europe and other areas as an antidiarrheal agent. We have previously shown in a placebo-controlled double-blind clinical trial that *S. boulardii* reduced antibiotic-associated diarrhea in man (11) and *C. difficile*-associated cecitis in hamsters (12). Based on these findings, we evaluated the hypothesis that *S. boulardii* would prevent *C. difficile* overgrowth following vancomycin treatment of *C. difficile*-associated cecitis in a hamster model (13). The latter study simulated recurrence of human *C. difficile*-associated colitis in that a normally lethal dose of clindamycin was given, followed by 10 days of vancomycin. Hamsters given *S. boulardii* had lower concentration of *C. difficile* and lower cytotoxin titers than animals given only water (13). These results prompted us to enrol a small number of patients with recurring *C. difficile* colitis in an open trial using *S. boulardii* to test whether the yeast would treat further recurrences when used in conjunction with vancomycin.

METHODS

Patients with an initial occurrence of PMC and one or more subsequent recurrence(s) of *C. difficile* diarrhea were referred by physicians in the Seattle area. Patients had been successfully treated with vancomycin or metronidazole, but had at least one recurrence of diarrhea after anti-clostridial treatment stopped. Eligible patients had positive *C. difficile* stool cultures and also were cytotoxin positive. At enrolment, patients filled out a standardized history form, underwent a physical examination, and had stools tested for *C. difficile* culture and cytotoxin. Standard therapy with vancomycin (250 mg orally qid for 10 days) was then initiated. *S. boulardii* (2-250 mg capsules bid) was given on approximately the 5th day of vancomycin treatment and was continued for 30 days. At the end of *S. boulardii* treatment, stool cultures for *C. difficile* were taken. Success was defined as no recurrence of diarrhea during the period of *S. boulardii* treatment. Diarrhea was defined as three or more loose or liquid stools per day for at least two consecutive days. The study was approved by the University of Washington Human Subjects Review Committee.

S. boulardii was provided in capsules of lyophilized yeast by Laboratories Biocodex, Montrouge, France.

RESULTS

Medical history

The 13 enrolled patients had a mean of 3.6 ± 2.3 recurrences before study entry (range 1-9). The most frequently incriminated antibiotics for the induction of the first episode reported by 11 patients were non-ampicillin penicillins (n = 4, 36%) and cephalosporins (n = 3, 27%). Other agents used were: ampicillin (n = 2), augmentin (n = 1), and erythromycin (n = 1). Most patients previously had been treated with both vancomycin and metronidazole (n = 9, 69%), whereas two (15%) had been treated with only metronidazole, and two (l5%) had been treated with vancomycin alone. A history of recent surgery was reported by eight (62%) of the enrolled patients.

Colitis recurrence

Fourteen patients with recurring *C. difficile* colitis were enrolled, and 13 successfully completed the study (one patient only received 12 days of study drug and was dropped). Patients received a mean of 40 ± 21 days of *S. boulardii*, with all but two receiving 30-33 days of the study drug. Two patients received 74 and 98 days of *S. boulardii* by physician preference. The number of bowel movements was significantly decreased from a mean of 4.5 ± 2.6/day before *S. boulardii* treatment to a mean of 2.4 ± 1.2/day during *S. boulardii* treatment (t test = 2.6, $p = 0.03$). Of the 13 patients treated with *S. boulardii*, 11 (85%) reported no further recurrences, whereas two (15%) failed during *S. boulardii* treatment. Symptoms indicative of severe diarrhea or colitis (fever, abdominal pain, diarrhea, etc.) resolved after vancomycin with *S. boulardii* treatment in all patients except for the two patients who failed (diarrhea and abdominal pain continued). Patient characteristics of those who were successfully treated were compared with the patients who failed (Table 1).

The 11 patients who were successfully treated with *S. boulardii* were followed during the time of *S. boulardii* treatment and did not develop recurrent diarrhea. Of the seven patients we were able to contact after *S. boulardii* cessation, none reported recurrent diarrhea (range 2-150 days, median 6 days).

C. difficile

The presence of *C. difficile* was determined before and after vancomycin treatment. All 13 patients had detectable *C. difficile* cytotoxin in their stools at study enrolment. Eleven patients had stools cultured for *C. difficile* after vancomycin was stopped. Five patients were tested near the end of *S. boulardii* treatment (mean of 8 days before cessation), and seven patients provided stool samples post-study drug cessation (mean of 10 days). Of the 11 patients with post-vancomycin cultures (Table 2), significantly more were culture negative (55%, Fisher's exact test, $p = 0.02$) and cytotoxin negative (82%, Fishers Exact Test, $p < 0.001$) after treatment with vancomycin and *S. boulardii* than before treatment.

DISCUSSION

Previous studies commonly report that the frequency of recurrence of *C. difficile* colitis after an initial antibiotic treatment is 20% (6, 7), although the range in the literature varies from 6% to 53% (3, 4). Patients who have one recurrence are even more likely to have another recurrence (4, 5). The frequency of pre-study recurrences in this patient population (mean = 3.6 ± 2.3) supports this pattern of multiple recurrences, and emphasizes the need to establish an effective treatment modality. Traditional approaches to treating patients with recurring *C. difficile* colitis have included repeated courses of antibiotics (14), addition of resins such as cholestyramine and cholestipol (14, 15), the use of *Lactobacillus* (10), and longer tapering doses or pulse doses of vancomycin (4, 14). Prolonged treatment with vancomycin does not clear the colon of *C. difficile* spores and, thus, patients are at risk for recurrence as soon as the antibiotic is stopped (1, 3).

TABLE 1

Comparison of Factors of Patients with and without Subsequent Colitis Recurrences after Treatment with Vancomycin and S. boulardii

Factor	Patients with No Recurrences (successes)	Patients with Recurrences (failures)
No. of patients	11	2
Mean age (yr)	55 ± 15	64 ± 17
Female sex	7 (64%)	2 (100%)
Mean no. of pretreatment recurrences	3.2 ± 1.7	6.0 ± 4.2
C. difficile culture positive after treatment	3 (33%)	2 (100%)
C. difficile cytotoxin positive after treatment	1 (11%)	1 (50%)

TABLE 2

C. difficile Clearance by Combined Treatment with Vancomycin and S. boulardii

	C. difficile Culture	*C. difficile* Cytotoxin
Positive before treatment*	11	11
Positive after treatment*	5	2

Two patients with no post-vancomycin stool samples were excluded.

Indeed, two studies have shown that patients who are likely to have a recurrence are those in whom vancomycin failed to clear *C. difficile* from the colon (1, 3). A logical approach to the prevention of recurrences is to identify and correct the mechanisms that lead to recurrence (16).

The use of *S. boulardii* in this difficult clinical problem was based on animal studies showing a significant decrease in mortality and *C. difficile* cytotoxin titers in hamsters pre-treated with *S. boulardii* in the vancomycin withdrawal model (13). In our study, the use of *S. boulardii* after vancomycin treatment was successful in 85% of the patients who were experiencing multiple recurrences. The group of patients who were successfully treated and the patients who failed were compared, but conclusions are limited, due to the small number of patients who failed. Interestingly, neither of the patients who failed responded to the current vancomycin treatment: both had stool cultures positive for *C. difficile* after vancomycin and *S. boulardii* treatment, and one patient had recently received radiation therapy. These patients might have benefited from a longer duration of both treatments or a higher dose of *S. boulardii*.

The mechanism of action of *S. boulardii* has not been established in humans, but in animal models, *S. boulardii* inhibits the growth of *C. difficile* and decreases cytotoxin titers (13), thus inhibiting further *C. difficile* overgrowth and recurrence. It is important to note that *S. boulardii* was given in conjunction with vancomycin, and continued after the vancomycin was stopped. The efficacy of *S. boulardii* may be dependent on the ability of vancomycin to clear or reduce the concentration of *C. difficile* in the colon before *S. boulardii* is introduced. For this reason, *S. boulardii* treatment was initiated 5 days after vancomycin treatment.

In summary, *S. boulardii* represents a possible therapy for the treatment of recurring *C. difficile* diarrhea and colitis. Controlled clinical trials on recurring *C. difficile*-associated colitis are needed to confirm its efficacy.

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