

Recurrent *Clostridium difficile*-Associated Diarrhea and Colitis Treated with *Saccharomyces cerevisiae* (Baker's Yeast) in Combination with Antibiotic Therapy: A Case Report

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Antibiotic-associated diarrhea is common in both inpatient and outpatient settings, and 15% to 20% of the cases are caused by *Clostridium difficile*.¹ Although antibiotic therapy with metronidazole or other agents is effective for most patients with *C difficile*-associated diarrhea, approximately 10% to 20% of patients receiving treatment for *C difficile* infection will experience a relapse following discontinuation of initial therapy,² and relapses are often multiple. This clinical problem can be frequent and frustrating.

C difficile-associated diarrhea is thought to occur when an alteration of the normal bacterial flora of the intestinal tract permits proliferation of toxigenic strains of *C difficile*. Various microorganisms have been used therapeutically to repopulate the intestinal flora to enhance resistance against *C difficile*. A randomized placebo-controlled trial has shown that the yeast *Saccharomyces boulardii* is effective for the treatment of recurrent *C difficile* disease.³ This biotherapeutic agent, however, is not available as a pharmaceutical preparation in the United States. We report herein a case of *C difficile*-associated diarrhea with multiple relapses that responded to treatment with antibiotics together with a commercial baker's yeast (Fleischmann's Yeast), which contains the closely related species *Saccharomyces cerevisiae* at a concentration of organisms at 10^{10} /g.

Case Report

A 50-year-old woman came to the office complaining of a 1-week history of diarrhea and weakness with crampy lower abdominal pain and 4 days of

vomiting and low-grade fever. One month earlier she had undergone a laparotomy with hysterectomy and bilateral salpingo-oophorectomy for drainage of a large pelvic abscess. She had received intravenous antibiotics during her hospitalization and was sent home from the hospital with a prescription for oral clindamycin, 300 mg four times a day, which she had taken for 20 days.

The patient was given a prescription for oral metronidazole for a presumptive diagnosis of antibiotic-associated colitis, but she required hospitalization the following day because of intractable vomiting and abdominal pain. A stool sample was guaiac negative, but it was positive for *C difficile* by enzyme-linked fluorescent immunoassay (ELFA) performed with the automated VIDAS instrument and CDA Dual Reagent Strips (bioMérieux Vitek, Inc., Hazelwood, Mo). Her white blood cell count was $7300/\mu\text{L}$. A bowel obstruction series was negative, and a computed tomographic scan of the abdomen and pelvis showed no evidence of recurrent abscess. She continued to vomit when given oral metronidazole, so she was given intravenous metronidazole and oral vancomycin for 4 days. She was released from the hospital with instructions to continue taking vancomycin, 125 mg four times a day, for 5 more days.

Several days after discharge she developed hives, and the vancomycin was stopped. A few days later she developed recurrent diarrhea. Oral metronidazole was started, but she developed nausea, vomiting, and abdominal cramping. The metronidazole was stopped on the suspicion that these symptoms might be side effects, and cholestyramine was prescribed. After a day or 2 she developed severe abdominal cramping, and the cholestyramine was stopped. The vancomycin was restarted without recurrent hives, but she continued to have nausea, vomiting, and diarrhea, and she was readmitted to the hospital. She was given intravenous metronida-

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zole for 6 days. Her *C difficile* toxin assay was again positive, and a sigmoidoscopic examination showed classic-appearing pseudomembranes. After she was sent home from the hospital, she continued taking oral vancomycin for about 2 weeks.

One week after stopping the vancomycin she noted recurrence of nausea and the following day developed diarrhea. The vancomycin was started again, but because of the vomiting, she was admitted for the third time for colitis. Treatment was started with intravenous metronidazole, and she responded quickly. She was released from the hospital with a prescription for vancomycin, 125 mg four times a day for 10 days, then twice a day for 7 days, then every other day for 3 weeks, along with a lactobacilli preparation (Lactinex) 1 g four times a day for 3 weeks.

Two weeks later the patient was readmitted a fourth time, just 2 days after switching to the twice-a-day regimen, with vomiting and abdominal discomfort. Although she had not yet developed diarrhea, she believed her symptoms were the same as with previous relapses. Findings of a repeat sigmoidoscopy to 30 cm were normal. An infectious disease consultant recommended treatment with *Saccharomyces cerevisiae* (Fleischmann's Yeast) 1/8 tsp, four times a day for 4 months, and vancomycin 125 mg four times a day for 30 days. With this course of treatment there have been no further recurrences in more than 3 years.

Discussion

C difficile is a spore-forming obligate anaerobic bacillus and is a component of normal fecal flora in about 5% of healthy adults. It can be found in the stool of 10% or more of hospitalized adults without diarrhea who have received antibiotics or chemotherapeutic agents. In *C difficile* diarrhea, colitis both with and without pseudomembranes is due to toxin-mediated mucosal inflammation. The most commonly implicated antibiotics are ampicillin and other penicillin derivatives, cephalosporins, and clindamycin.

The typical clinical manifestations of *C difficile* diarrhea are crampy abdominal pain, profuse diarrhea, low-grade fever, and leukocytosis. The onset can be as soon as after a few days of antibiotic therapy, or it might be delayed for up to 8 weeks after its discontinuation. Fever can be as high as 40°C, and leukocytosis can reach 50,000/ μ L.² The

colitis is usually most severe in the distal colon and rectum, but it can occur throughout the colon. Colitis localized to the cecum might cause little or no diarrhea, but it can cause fever, marked right lower quadrant abdominal pain and tenderness, marked leukocytosis, and decreased intestinal motility.⁴

Endoscopy with biopsy of suspect lesions is the most rapid way to establish the diagnosis of *C difficile* colitis. The characteristic lesions are raised, yellowish nodules or plaque-like pseudomembranes, often with skip areas of normal mucosa. Typical pseudomembranes are often absent, however. Tissue culture tests for toxin B are the reference standard and can detect the specific cytopathic effects of toxin B in more than 90% of patients with pseudomembranous colitis. A negative test, however, does not rule out *C difficile* as the cause of diarrhea. It is also not uncommon for patients to continue to have positive tests for toxin B or the organism after otherwise successful therapy. Enzyme immunoassay tests for toxin A or B are the most widely used tests to diagnose *C difficile* infection. They are more specific than they are sensitive, with sensitivities ranging from 70% to 95%. The sensitivity can be improved by sending a second stool sample the next day, rather than the same day.¹ Stool cultures for *C difficile* can yield false-positive results in patients with simple antibiotic-induced diarrhea who have coincidental colonization with *C difficile*. The finding of fecal neutrophils raises the suspicion of *C difficile*-associated diarrhea.

Treatment of *C difficile*-associated diarrhea includes supportive therapy with replacement of fluids and electrolytes. The patient should stop taking antibiotics, if possible. Treatment with antiperistaltic or opiate antidiarrheal agents should be avoided. Metronidazole, preferably given orally, is the drug of choice for treating *C difficile*-associated diarrhea. The usual dose of oral metronidazole is 250 mg four times a day for 10 days.

Vancomycin was prescribed for the patient reported above because she was unable to tolerate oral metronidazole. Vancomycin is to be discouraged, however, so as not to promote the spread of vancomycin-resistant enterococci and staphylococci.⁵ Vancomycin is also much more expensive and proved no more effective than metronidazole in a prospective randomized trial comparing the two agents.⁶

Relapses or recurrences, defined as the return of symptoms, signs, and positive diagnostic tests a few weeks to months after discontinuing successful treatment of *C difficile* diarrhea, are common, and occur in 15% to 35% of patients.¹ As in this case, relapses usually respond well to treatment, but multiple recurrences are common, and up to 20 have been reported in a single patient.

Metronidazole and vancomycin do not reliably kill the spore forms of *C difficile*; in fact, they might encourage the formation of spores. The persistence of both the spores and the antibiotic-induced reduction of the colonic bacterial flora presumably account for the propensity for relapse.

There is no specific regimen that has been clearly proved to prevent recurrences. Longer courses of metronidazole or vancomycin therapy have been tried, sometimes with every-other-day administration or gradual tapering. *Lactobacillus* preparations or yogurt with live cultures are sometimes tried. Two small open trials involving a total of 9 patients have suggested that *Lactobacillus casei* GG might be effective for the treatment of recurrent *C difficile* colitis.^{7,8}

The decision to use yeast to treat *C difficile*-associated diarrhea in our patient was based on a promising randomized, double-blind, controlled study using live yeast (*Saccharomyces boulardii*) to treat *C difficile*-related diarrhea.³ In that study, the addition of *S boulardii* to standard antibiotic treatment in 60 patients with recurrent *C difficile* disease reduced the subsequent relapse rate by about 50% when compared with placebo plus antibiotics. In 64 patients with *C difficile* disease initially, there was no significant difference in benefit with the addition of *S boulardii*, although because so few patients with initial disease failed, there was only a 10% power of detecting a significant difference. Patients who were immunocompromised as a result of AIDS or cancer chemotherapy were excluded from the study. The two adverse reactions noted with *S boulardii* were increased thirst and constipation. Because *S boulardii* is not readily available in the United States, some physicians have tried *S cerevisiae* (baker's yeast, found in Fleischmann's Yeast) with anecdotal success.⁹ The principal author of the *S boulardii* study, however, responded to this report with the assertion that *S cerevisiae* is a completely different species and cited controlled experiments in mice where *S boulardii* showed a signifi-

cant protective effect against *C difficile* whereas *S cerevisiae* did not.¹⁰

Conclusion

A case of well-documented *C difficile* diarrhea with four recurrences is described in which a novel and unproved variation of a yeast-based therapy given with a more prolonged course of oral vancomycin was followed by no further recurrences. Whereas no conclusions can be made about the efficacy of *S cerevisiae* for preventing recurrences of *C difficile* diarrhea, this case left a strong impression. Further study of this inexpensive and readily available treatment should be considered.

Ernest Davis, DO, the infectious disease consultant, recommended the use of baker's yeast in this case.

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