

Treatment of Recurrent *Clostridium difficile* Diarrhea

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Abstract: Treatment of recurrent *Clostridium difficile*-associated diarrhea can be challenging. Once patients develop recurrent disease, further episodes are common and can continue for months or even a year or more. Treatment begins with a repeat standard 10-day course of antibiotics, followed by tapering and/or pulsing of the antibiotic dose. Probiotics can also be useful, particularly the nonpathogenic yeast *Saccharomyces boulardii*. Stool reconstitution via fecal enemas, colonoscopy, and nasogastric tubes have been performed to restore normal colonic flora. Additional approaches under investigation, such as vaccination against *C. difficile*, show encouraging preliminary results.

C*lostridium difficile* is a Gram-positive anaerobic bacillus that is the most common cause of nosocomial diarrhea, resulting in substantial morbidity and mortality. Transmission occurs via the fecal-oral route by ingestion of spores that germinate into bacteria. Colonization usually occurs after the normal flora has been disrupted by antibiotic therapy, although sporadic cases can occur.¹ The bacterium produces two toxins, A and B, that are responsible for the ensuing diarrhea and colitis. Recent epidemics have been associated with a fluoroquinolone-resistant strain that produces a binary toxin, the significance of which is unclear.^{2,3} The spectrum of disease ranges from asymptomatic carriage to severe pseudomembranous colitis, often occurring 1–2 weeks after the initiation of antibiotic therapy.

Although patients with an initial episode of *C. difficile*-associated disease (CDAD) usually respond to antibiotic therapy, 20–35% of patients will develop recurrent disease.^{4,6} Most recurrences occur within 5–8 days of completion of therapy. Once recurrent *C. difficile*-associated disease (RCDAD) develops, 45–65% of patients will have repeated episodes that can continue for months or, rarely, for several years.^{7,8} Risk factors for recurrent disease include continued use of antibiotics, advanced age, female sex, and renal disease.^{4,9} The pathophysiology is not fully defined, but may be explained by an inability of the normal flora to repopulate the colon and suppress

Keywords

Recurrent *Clostridium difficile*-associated disease, vancomycin, metronidazole, *Saccharomyces boulardii*, *Lactobacillus* GG.

overgrowth of *C. difficile* or by an inadequate immune response or both. Although the term “relapse” implies the presence of the same strain, studies comparing *C. difficile* strains from initial and recurrent episodes have shown that in 25–67% of cases the recurrent strain is a different one.^{5,10–12} It is likely that other factors affect the likelihood of recurrence, including the abnormal flora and an altered host immune response.

The diagnosis of RCDAD is based on the detection of *C. difficile* and/or toxin in the stool of patients with diarrhea that recurs after completion of the initial antibiotic for CDAD. Symptoms can be severe, and approximately 6–10% of patients with RCDAD are hospitalized during serious episodes. In this situation other causes of diarrhea, although uncommon, should be considered. Postinfectious irritable bowel syndrome can contribute to chronic diarrhea syndromes, as can postinfectious inflammatory bowel disease or microscopic colitis.

Treatment of RCDAD presents a challenge. Once a patient has a recurrence, the chance of future recurrences is markedly increased,⁴ and there is no uniformly effective therapy. Current treatment options include repeat antibiotics, which should be given to all patients, as well as several microbiological and immune approaches for adjunctive therapy.

Repeat Antibiotics

An initial approach to RCDAD involves the use of antibiotics, typically metronidazole 250 mg orally four times daily for 10 days, or vancomycin 125–500 mg orally four times daily for 10 days. Rifampin is occasionally used as adjunctive therapy, although no controlled studies have demonstrated superiority.¹³ It is important to realize that recurrence is not due to resistance of the organism to the treating antibiotic. Recurrences are decreased by tapering or pulsing antibiotics. With tapering, doses are gradually decreased over a period of several days. Due to the possibility of developing irreversible peripheral neurotoxicity with long-term metronidazole, vancomycin is often preferred. Pulse therapy involves alternating antibiotics with days off of therapy, which occur at increasing intervals. A combination approach is to taper antibiotic doses initially over 2–3 days after the initial 10-day treatment, followed by pulse therapy at that dose for several weeks. In one study of 163 patients with RCDAD, recurrences occurred in 40–71% of patients following a 10- to 14-day course of antibiotics, compared to recurrence rates of 31% with a tapering regimen, 14% with pulsing, and 20% with a combination approach.¹⁴

A sample antibiotic regimen for RCDAD might consist of vancomycin 500 mg four times daily for 10 days, followed by a lower dose of 125 or 250 mg twice daily

every other day for a week, then every third day, etc. Once antibiotics are taken only every tenth day, recurrences are unlikely and antibiotics can be discontinued.

Probiotics

The term “probiotic” refers to a microorganism whose ingestion leads to a beneficial therapeutic effect, in this case by presumably allowing the normal flora to repopulate and suppress overgrowth of *C. difficile*. Proposed mechanisms by which this might occur include competition for nutrients, stimulation of immunity, inhibition of mucosal adherence, and production of antimicrobial substances.¹⁵ Probiotics have gained popularity, initially in Europe and more recently in the United States. Both bacteria and yeast have been used in the treatment of RCDAD, although only the yeast *Saccharomyces boulardii* has been shown to be effective in randomized controlled trials.

Saccharomyces boulardii

S. boulardii is a nonpathogenic yeast with an unusual optimum growth temperature of 37°C. It survives passage through the gastrointestinal tract, and reaches steady-state levels in the stool of human volunteers within 3–5 days.¹⁶ Oral administration is well tolerated, and it has been used in Europe for many years for the prevention of antibiotic-associated diarrhea. Several controlled trials have shown efficacy in this setting.^{17–19} In a hamster model of RCDAD, *S. boulardii* was found to prevent recurrence of clindamycin-induced cecitis.²⁰ These results prompted the enrollment of 14 patients with RCDAD into an open-label trial of *S. boulardii* plus vancomycin. Of the 13 patients that completed the study, 11 (85%) had no further recurrences.²¹ Subsequently a randomized controlled trial was performed in which *S. boulardii* was given with vancomycin or metronidazole to 64 patients with an initial episode of CDAD and 60 patients with RCDAD. Treatment resulted in no significant improvement in patients with initial CDAD, but decreased recurrences by almost 50% in those with recurrent disease.²² Neither the dose nor duration of antibiotics was controlled for in this study.

In a later trial, patients received a standard 10-day regimen of high-dose vancomycin (2 g/day), low-dose vancomycin (500 mg/day), or metronidazole (1 g/day) plus either *S. boulardii* or placebo. A significant reduction in recurrences was seen only in the group receiving *S. boulardii* and high-dose vancomycin.²³ One explanation might be improved clearance of *C. difficile* from the stool by high-dose vancomycin. In fact, treatment with high-dose vancomycin completely cleared *C. difficile* by the end of the 10-day course of antibiotic therapy, whereas the other antibiotic regimens did not. Similar results have

been reported elsewhere, with *C. difficile* clearance in 89% of patients receiving vancomycin versus 59% of those treated with metronidazole.¹⁴ Another potential explanation is the protease produced by *S. boulardii*, which inactivates *C. difficile* toxin receptors and results in proteolytic digestion of toxins A and B.^{24,25} The authors hypothesized that by preventing binding of *C. difficile* toxin, this protease might allow for restoration of the normal intestinal microflora and reestablishment of colonization resistance. Other potential mechanisms of action of the *S. boulardii* protease have been suggested by animal studies, which show diminished ileal fluid secretion in rats exposed to *C. difficile* toxin A²⁵ and stimulation of the intestinal immunoglobulin (Ig) A response to toxin A in mice.²⁶

Lactobacillus

Lactobacillus GG has several characteristics that make it an appealing probiotic. It is resistant to acid and bile, allowing it to survive passage through the gastrointestinal tract.²⁷ It adheres to intestinal epithelial cells and produces an antimicrobial substance that inhibits a broad range of bacteria, including *C. difficile*.²⁸ Uncontrolled trials have suggested efficacy in RCDAD. In one report, 4 out of 5 patients had an immediate response to therapy and had no further relapses. The fifth patient required two courses of *Lactobacillus* GG to achieve cure.²⁹ Additional uncontrolled trials reported cure in 2 out of 4 children³⁰ and 5 out of 9 adults.³¹ Although a preliminary report of a controlled trial also suggested efficacy, no final report has been published.³² A randomized, controlled trial evaluating the addition of *Lactobacillus plantarum* 299v to metronidazole therapy was not adequately powered to show a significant benefit; recurrence occurred in 4 out of 11 patients receiving combination therapy, compared to 6 out of 9 patients receiving metronidazole and placebo.³³

Fecal Enemas and Stool Repopulation

Several reports have described the use of stool donation in an attempt to replenish the colon with healthy bacteria. In one of the earliest reports, Bowden and colleagues³⁴ suggested that bacterial overgrowth plays an important role in the development of pseudomembranous colitis, and postulated that restoration of fecal floral homeostasis could lead to resolution of disease. In this study, 16 patients who had failed standard therapy for pseudomembranous enterocolitis were treated with fecal enemas derived from the stool of family members or other healthy volunteers. Thirteen had a dramatic clinical response with no reported side effects. The remaining three patients died. Of these three, two did not have pseudomembranes at death, and one had small bowel involvement.

Other authors have used a similar approach for RCDAD. Schwan and colleagues³⁵ reported successful

treatment of RCDAD by rectal infusion of normal feces in a woman who had experienced multiple relapses of *C. difficile* colitis. Persky and Brandt³⁶ reported success in another patient, using infusion of stool donated from the patient's husband and injected at 10 cm intervals throughout the colon during colonoscopy. They hypothesized that polyethylene glycol and electrolyte solution (Golytely, Braintree) preparation may have helped as well by allowing elimination of residual *C. difficile* organisms and spores before stool administration. They also suggested that administration during colonoscopy may be more effective than by enema, due to the ability to administer organisms proximal to the splenic flexure.

Donor stool has also been administered via nasogastric tube into the stomach. Aas and associates³⁷ performed a retrospective review of 18 patients treated in this manner over a 9-year period. Patients were pretreated with at least 4 days of oral vancomycin. In the subsequent 90 days following stool transplantation, 2 patients died of unrelated illnesses, and only 1 of the remaining patients experienced recurrence of *C. difficile* colitis.

Rectal Instillates of Microbes

Tvede and Rask-Madsen³⁸ studied 6 patients with chronic RCDAD, and found that rectal instillation of a mixture of facultative aerobic and anaerobic bacteria led to loss of *C. difficile* and its toxin from the stools.³⁸ It also led to bowel colonization by *Bacteroides* species, which had not been present in pretreatment stool samples. This suggests that *Bacteroides* may play a role in maintaining the normal intestinal milieu.

Nontoxicogenic Strains of *C. difficile*

Borriello and Barclay³⁶ studied the use of nontoxicogenic strains of *C. difficile* using a hamster model of RCDAD. Hamsters pretreated with nontoxicogenic strains prior to clindamycin therapy were protected against the development of *C. difficile* diarrhea.³⁹ Most of the protected hamsters survived for up to 27 days, compared to none of the controls. These strains were later given orally to two humans with RCDAD, with resolution of their symptoms.⁴⁰ However, a recent report of nontoxicogenic strains of *C. difficile* among hospitalized patients with diarrhea suggests that nontoxicogenic strains may also cause diarrhea, making this treatment approach less appealing.⁴¹

Toxin Binders

Another adjunctive therapeutic approach is the use of anion exchange resins, including cholestyramine and colestipol, in an attempt to bind *C. difficile* toxins. Efficacy of these agents in toxin binding has not been clearly estab-

lished. Anion exchange resins have been given to patients with pseudomembranous colitis with variable response.⁴²⁻⁴⁴ In RCDAD, colestipol was given in combination with tapering doses of vancomycin to 11 patients, with resolution of symptoms and no recurrence for at least 6 weeks.⁴⁵ Because these agents can also bind antimicrobials, they should not be given within 2–3 hours of antibiotic ingestion. Synthetic toxin binders have also been studied, and have been shown to have efficacy in binding *C. difficile* toxins,⁴⁶⁻⁴⁷ but are still in clinical trials.

Immune Approaches

Immune approaches to the treatment of RCDAD have included both active and passive immunization against *C. difficile*.⁴⁸ This concept stems from studies that suggest a defective humoral response to the organism in patients with recurrent disease. Warny and coworkers⁴⁹ found that patients with RCDAD had significantly lower serum IgG and fecal IgA antitoxin A titers than did patients suffering a single episode. Antibody levels also appeared to affect the duration of symptoms, such that patients with symptoms lasting more than 2 weeks had significantly lower antibody levels than those with symptoms of shorter duration. Aronsson and associates⁵⁰ found a correlation between high IgG titers to toxin B and clinical recovery without relapse. In a study of 6 children with RCDAD, Leung and colleagues⁵¹ found lower IgG antitoxin A levels in those with relapsing disease.

Further evidence suggests that the immune response may determine whether patients with nosocomial infection develop diarrhea or remain asymptomatic. Kyne and colleagues⁵² studied antibody response to *C. difficile* toxin and found that although antibody levels did not correlate with the likelihood of colonization, patients who remained asymptomatic carriers had significantly higher serum levels of IgG antibody against toxin A than patients that developed diarrhea. This group later reported that patients with RCDAD had lower concentrations of serum IgM against toxin A on day 3 and of IgG to toxin A on day 12 after the onset of symptoms.⁵³ Thus, it appears that serum antibodies to toxin A provide protection from *C. difficile* diarrhea and from the development of recurrent disease in humans.

Therapeutic measures have included active and passive vaccination. Aboudola et al⁵⁴ developed a parenteral vaccine to inactivated toxins A and B, and showed that it led to high antibody levels in healthy volunteers. The vaccine was then given in combination with vancomycin to three patients with multiple episodes of RCDAD without further recurrence.⁵⁵

Another approach is passive immunization using intravenous immunoglobulin (IVIG). This has been

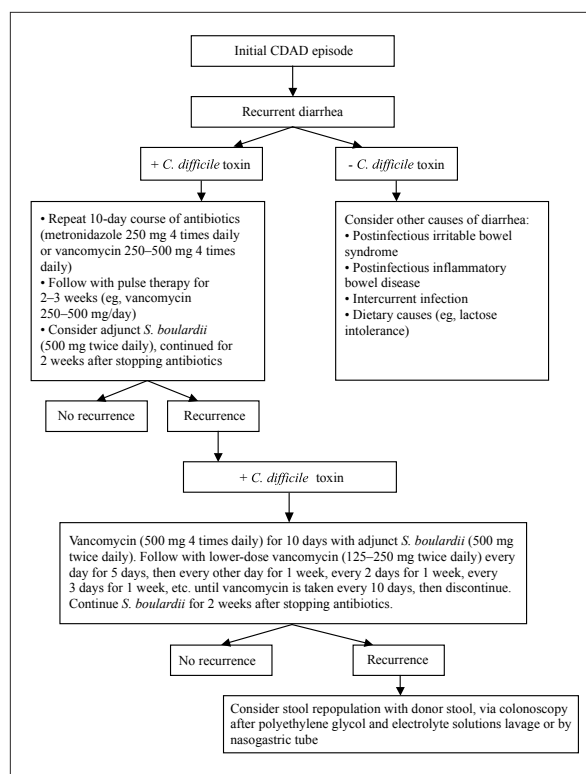


Figure 1. Treatment strategy for recurrent *Clostridium difficile*-associated disease.

CDAD = *C. difficile*-associated disease; *S. bouardii* = *Saccharomyces bouardii*.

given with success to 5 children with RCDAD.⁵¹ Patients responded with significant increases in IgG antitoxin A levels and clinical resolution of gastrointestinal symptoms. Success has also been reported with IVIG in adults.^{56,57} Wilcox⁵⁸ treated 5 patients with protracted or recurrent CDAD using IVIG at doses of 300–500 mg/kg. Three had a good response, 1 had recurrence, and 1 died of intractable CDAD.

Oral antibodies may also be effective. Immunoglobulins derived from the colostrum of cows immunized with *C. difficile* toxoids have been found to neutralize the effects of toxins A and B in vitro, and to inhibit enterotoxic effects in the rat ileum.⁵⁹ In hamsters, these immunoglobulins prevent diarrhea and subsequent death.⁶⁰ Avian antibodies against recombinant toxins have also been shown to be effective in a hamster model.⁶¹ In a recent pilot study in humans, whey protein concentrate (WPC) containing high concentrations of IgA antibodies derived from the milk of *C. difficile*-immunized cows was given to 16 patients with CDAD. Nine of these patients had RCDAD. Patients were treated with standard antibiotics followed by WPC for 2 weeks, and none suffered further

episodes of diarrhea.⁶² A randomized controlled trial using WPC is underway.

Bowel Irrigation

Whole-bowel irrigation with polyethylene glycol solution was given to two children with RCDAD who had failed several therapeutic regimens.⁶³ Treatment was followed by a 3-week course of oral vancomycin and *Lactobacillus* therapy. Both patients had a prompt response and no further recurrences. The authors postulated that whole-bowel irrigation cleared the intestine of *C. difficile* organisms, toxins, and spores. The extent to which the clinical response may have been due to polyethylene glycol remains unclear.

Conclusion

Treatment of RCDAD remains a challenge, although recent developments are encouraging. A therapeutic strategy for RCDAD might consist of a 10-day course of high-dose vancomycin (2 g/day) followed by pulse dosing at lower doses (250–500 mg/day), with gradually increasing intervals between days on and days off antibiotics (Figure 1). Efficacy can be improved by adding *S. boulardii* (500 mg twice daily) and continuing it for 2 weeks after cessation of antibiotics. If this is unsuccessful, a second attempt can be considered. Stool donation via colonoscopy is an option in the case of continued recurrence, although this approach has not been studied in controlled trials. Future treatment strategies may also incorporate immune approaches such as vaccination against *C. difficile*.

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