Breaking the Cycle: Treatment Strategies for 163 Cases of Recurrent *Clostridium difficile* Disease

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**OBJECTIVE:** There is currently uncertainty as to the best treatment for patients with recurrent episodes of *Clostridium difficile* disease (RCDD). Our objective was to evaluate the success of treatment strategies in a cohort of 163 RCDD patients.

**METHODS:** Data were used from patients who had participated in the placebo arm in two national referral clinical trials evaluating a new combination treatment. Patients with active RCCD were enrolled, prescribed either vancomycin or metronidazole, and randomized to either the investigational biological or a placebo. All patients were observed for at least 2 months for a subsequent episode of RCCD.

**RESULTS:** Of the 163 cases, 44.8% recurred. A tapering course of vancomycin resulted in significantly fewer recurrences (31%, *p* = 0.01), as did pulsed dosing of vancomycin (14.3%, *p* = 0.02). A trend (*p* = 0.09) for a lower recurrence frequency was observed for high-dose (≥2 g/day) vancomycin and low-dose (≤1 g/day) metronidazole. Vancomycin was significantly more effective in clearing *C. difficile* culture and/or toxin by the end of therapy than metronidazole (89% vs 59%, respectively; *p* < 0.001).

**CONCLUSIONS:** These data show that tapered or pulsed dosing regimens of vancomycin may result in a significantly better cure of RCDD. The persistence of *C. difficile* spores suggests that additional strategies to restore the normal colonic microflora may also be beneficial. (Am J Gastroenterol 2002;97:1769–1775. © 2002 by Am. Coll. of Gastroenterology)

**INTRODUCTION**

*Clostridium difficile* disease (CDD) has remained the most common cause of nosocomial GI infections despite discoveries involving its pathogenesis, epidemiology, and control measures (1, 2). The exact incidence of CDD is uncertain, as there are no specific established national surveillance programs; however, estimates may be made from several other national data banks. Based on data from the American Hospital Association (3), the National Hospital Discharge Summary (4), and the National Nosocomial Infections Surveillance System (5), the national prevalence of *C. difficile* infections may range from 9,229 to 107,486 cases/yr. In contrast, a recent review article (6) gave a range of 300,000–3 million cases of CDD a year, but this frequency was based on older studies of selected high risk populations. CDD may result in serious complications, including increased morbidity and mortality (7–11), longer hospital stays (2), and higher health care costs (8, 12, 13). Although patients suffering their first episodes of CDD are usually cured by standard antibiotic therapy (metronidazole or vancomycin), 20–35% of patients continue to experience recurrent episodes of CDD (RCDD) that are refractory to antibiotic therapy (14–17). Using the estimates from the annual prevalence of CDD given above, the prevalence of RCDD may range from 1,846 to 37,620 cases/yr (3–5).

Once RCDD develops, 45–65% continue to have repeated episodes that may continue over a period of several years (1, 7). RCDD is a serious disease that results in extended bouts of diarrhea necessitating long durations of antibiotic exposure. In one study, treatment of these recurrent episodes required an average of 265 additional days/patient of vancomycin and 19.7 days/patient of metronidazole to treat all the recurrent episodes (7) (unpublished data). RCDD has continued to be a clinical dilemma for both patients and their physicians.

Unfortunately, strategies to treat RCDD have relied upon studies based on patients with initial CDD or have been largely anecdotal. Most guidelines recommend repeated courses of vancomycin or metronidazole, but this often fails to stop the recurrence (1, 17, 18). The debate as to which antibiotic is more effective for RCDD lacks sufficient evidence for a firm conclusion to be drawn (19). Previous treatment studies either have not been in patients with RCDD exclusively or have been small case reports. For this reason, we evaluated a case cohort of placebo/antibiotic-treated patients from two trials to evaluate the efficacy of different antibiotic regimens for the treatment of RCDD.

**PATIENTS AND METHODS**

Cases of RCCD were collected from two national, double blind, placebo-controlled trials in adults with CDD testing for the safety and efficacy of an investigational biological, *Saccharomyces boulardii* (14, 20). The studies were approved by the institutional review board of each participat-
ing hospital or clinic, and each patient gave written informed consent. Patients were referred to the study by their primary physicians and were enrolled in the contiguous United States. All patients were tested for *C. difficile* and treated with either vancomycin or metronidazole and randomized to either *S. boulardii* (1 g/day for 28 days) or a placebo as an adjunct to the antibiotic. As the objective of this study was to evaluate the response to standard antibiotic placebo as an adjunct to the antibiotic. As the objective of this study was to evaluate the response to standard antibiotic treatment; positive 100 yr; occurrence of active diarrhea before standard antibiotic treatment; positive *C. difficile* assay (either by culture or by toxin A or B) during episodes of diarrhea; and one or more prior episodes of CDD within 1 yr. Exclusion criteria included active diarrhea due to a cause besides *C. difficile*, immunosuppression (AIDS or cancer chemotherapy within 3 months), negative enrollment *C. difficile* assays, receiving current oral antifungal therapy, or pregnancy.

Medical history and data on previous episodes were collected during the screening visit. Informed consent was obtained and stools were screened for *C. difficile* (culture or toxin A or B).

Eligible patients were then enrolled and treated with either vancomycin or metronidazole. In the first study the dose and duration of the antibiotic varied based upon the physician’s clinical assessment and the patient’s response to previous antibiotic treatments (14). In the second study, the choice of antibiotic treatments was limited to either low dose or high dose vancomycin (500 or 2 g/day for 10 days) or metronidazole (1 g/day for 10 days). If the patient failed the initial study’s antibiotic treatment, the patient was considered a treatment failure and the choice of the subsequent therapy was decided by the patient’s physician. Subsequent antibiotic treatments chosen by physicians included repeated 10- to 16-day courses of an antibiotic; a “tapered regimen” (dose of vancomycin or metronidazole started at one dose [500 mg to 3 g/day] and then decreased stepwise over a period of time to doses ranging from 125 to 750 mg/day); a “pulsed regimen,” which may or may not have followed a 10- to 14-day course of vancomycin, followed by a pulse of a dose of vancomycin (125–500 mg) every 2–3 days over a period of time (usually 3 wk); and a combination of the above.

Stool samples were assayed for *C. difficile* at enrollment, end of antibiotics, end of 4 wk, end of 8 wk, and any time of suspected recurrence of *C. difficile* diarrhea. Stools were assayed using standard culturing methods (selective *C. difficile* media plates and broths), cytotoxin tissue culture for toxin B, and enzyme immunoassay for toxin A as described previously (20). If a sufficient stool sample was collected, the stools were frozen (−20°C) and assayed for spores by heating at 80°C for 10 min before using standard culturing assays (21).

**Case Definitions**

*CDD* was defined as diarrhea (change in normal bowel habit with three or more loose or watery stools per day for at least 2 consecutive days or eight or more loose stools in 48 h) associated with one or more positive *C. difficile* assays (culture or toxin A or B) and not due to another etiology of diarrhea (stool pathogens, medications, active intestinal disease). *RCDD* was defined as a history of at least one CDD episode within the past year that had initially responded to antibiotic treatment. The lifetime duration of RCDD is defined as time from the first episode of CDD to the time of enrollment in the trial. The outcome of this analysis was determined by whether the patient had another *C. difficile* recurrence during the study subsequent to the enrollment episode, or if the patient was cured (did not have another recurrence) in the 2 months after antibiotics.

**Statistical Analysis**

The significance of the differences between continuous variables was assessed by the Student’s *t* test; if the variances were significantly different, a separate variance estimate was calculated. Nonparametric data were analyzed by means of the Wilcoxon ranked sum test (*U*). Significant differences between nominal variables were assessed by χ² analysis or Fisher’s exact test, by use of EPISTAT software (Gustafson, Round Rock, TX). Two-tailed tests of significance were used for all tests at a level of *p* < 0.05. The association between two variables was tested using a regression correlation coefficient (r²).

**RESULTS**

**Study Population**

There were 163 eligible cases of RCDD collected from the placebo arms of the two study populations (14, 20). RCDD patients were 18–91 yr old (mean = 61.6 ± 18.5), and 127 (77.9%) were female. The refractory nature of RCDD was reflected by their histories of CDD: the mean number of prior CDD episodes was 3.2 ± 2.1 (range = 1–14), and the total duration of their RCDDs ranged from 20 days to 4.0 yr (median = 113 days). The mean days of follow-up were 58.8 ± 10.5 for the patients given the typical 10- to 16-day course of antibiotics and longer (79.8 ± 5.6 days) for patients given tapered or pulsed doses.

Of the 163 patients with RCDD, who were required to have at least one positive *C. difficile* assay, enrollment cytotoxin assays for toxin B were positive most frequently. Of the 137 cytotoxin assays done on enrollment stool samples, 122 (89.0%) were positive; of 115 stools tested for toxin B, 85 (73.9%) were positive; and of 101 stools assayed...
by culture, only 50 (49.5%) were positive. In all 51 cases, when the enrollment culture was negative, either toxin A or toxin B was positive. There were eight cases at enrollment with negative toxin results, but C. difficile was found by culturing. All eight cases were included because the patients fulfilled the case definition of diarrhea and had abdominal pain and recent histories of prior episodes of toxin positive diarrhea. Three of the eight patients submitted additional stool samples within 48 h of the toxin negative samples, with subsequent positive toxin findings.

**Risk Factors for Recurrences**

Of the 163 cases enrolled and treated with standard antibiotics, 73 (44.8%) had at least one subsequent CDD recurrence during the study. The time until the next episode was relatively short. The “time until next episode” was measured from the last day of antibiotic therapy to the first day of the next documented CDD recurrence. The median time until next episode was 8 days, ranging from 1 to 42 days. Differences between the group of patients that had recurrences during the study and those who were cured are shown in Table 1. The mean ages did not significantly differ, but there was a trend for more female patients to have recurrences ($p = 0.08$). Patients who had recurrences did have significantly longer lifetime durations of RCDD (mean = 191 days) than those who did not have recurrences (mean = 131 days) ($p < 0.05$).

**Success of Antibiotic Treatments**

Of the 119 cases treated with vancomycin only, 46.2% recurred during the study; of 38 treated with metronidazole only, 42.1% recurred; and of six treated with either both antibiotics or vancomycin with another antibiotic (rifampin), 33.3% recurred. The overall failure rates between the antibiotic groups did not statistically differ ($X^2 = 0.53$, $p = 0.77$).

However, if the antibiotic regimens are further stratified, significant differences in response to treatment are observed (Table 2). There was a significant difference in the recurrence rate depending upon the type of vancomycin treatment given ($X^2 = 10.85$, $p = 0.05$). As shown in Figure 1, the highest recurrences were observed in patients given 1- to 2-wk courses of medium dose (1 g/day) vancomycin (71.4%), followed by low dose (500 mg/day) vancomycin (54.2%), followed by high dose (2 g/day) vancomycin (42.9%). Vancomycin tapered regimens and vancomycin pulsed dose regimens resulted in statistically significant reductions in the frequency of observed RCDD recurrences. Of the 29 patients given vancomycin as a decreasing tapered dose over a mean of 21.5 ± 10.0 days, only 31% ($p = 0.01$) had recurrences compared to the group with the highest frequency of recurrences. The doses used in the tapered regimen varied, as shown in Table 3, but the best responses were seen if the beginning dose was either 500 mg/day or 1

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### Table 1. Characteristics of Cases of RCDD by Treatment Outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Recurrence (n = 73)</th>
<th>Cure (n = 90)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ($\bar{x} \pm SD$)</td>
<td>62.5 ± 17.0</td>
<td>61.0 ± 19.6</td>
<td>&gt;0.05 (t = 0.51)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>62 (84.9%)</td>
<td>65 (72.2%)</td>
<td>0.08 ($X^2 = 3.08$)</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Duration of RCCD (days) ($\bar{x} \pm SD$)</td>
<td>191.3 ± 220.5</td>
<td>131.7 ± 110.0</td>
<td>&lt;0.05 (t = 2.22)</td>
</tr>
<tr>
<td>No. of prior CDD episodes ($\bar{x} \pm SD$)</td>
<td>3.6 ± 2.4</td>
<td>2.8 ± 1.7</td>
<td>&gt;0.05 (t = 0.28)</td>
</tr>
</tbody>
</table>

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### Table 2. Response to Treatment in Patients With RCDD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recurrence (n = 73)</th>
<th>Cure (n = 90)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium dose (1, &lt;2 g/day)</td>
<td>10 (71.4%)</td>
<td>4</td>
<td>*</td>
</tr>
<tr>
<td>Low dose (&lt;1 g/day)</td>
<td>26 (54.2%)</td>
<td>22</td>
<td>0.20</td>
</tr>
<tr>
<td>High dose (≥2 g/day)</td>
<td>9 (42.9%)</td>
<td>12</td>
<td>0.09</td>
</tr>
<tr>
<td>Taper</td>
<td>9 (31%)</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Pulse</td>
<td>1 (14.3%)</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>+other†</td>
<td>2</td>
<td>4</td>
<td>0.14</td>
</tr>
<tr>
<td>All</td>
<td>57/125 (45.6%)</td>
<td></td>
<td>0.85 ($X^2 = 0.04$)‡</td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose (≤1 g/day)</td>
<td>13 (44.8%)</td>
<td>16</td>
<td>0.09</td>
</tr>
<tr>
<td>Medium dose (1.5 g/day)</td>
<td>2 (40%)</td>
<td>3</td>
<td>0.24</td>
</tr>
<tr>
<td>High dose (2 g/day)</td>
<td>0 (0%)</td>
<td>2</td>
<td>0.12</td>
</tr>
<tr>
<td>Taper</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>16/38 (42.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Comparison group, Fisher’s exact test.
† Includes vancomycin + rifampin (n = 3) and vancomycin + metronidazole (n = 3).
‡ All vancomycin compared to all metronidazole.
g/day of vancomycin and the dose was tapered down to 125 mg/day. Vancomycin was tapered down over a mean period of 19–25 days. Of the 29 patients treated with tapering doses of vancomycin, 10 had following short courses of pulsed doses (125–500 mg/day every 2–3 days) of vancomycin. Of those 10 patients, 20% had recurrences during the study. Patients who had recurrences after pulsed dosing was completed had the pulses over a shorter time (3 days) than the patients who were cured (pulsed doses over a mean of 6 days), but this difference did not reach statistical significance.

As shown in Table 3, seven patients had pulsed doses (with no tapering of vancomycin), and significantly fewer of these patients had recurrences (14.3%, \( p = 0.02 \)). The patients who had recurrences on pulsed dosing were also given the pulses for a shorter time (9 days) than those who were cured (mean = 20.3 ± 11.1 days), but this difference did not reach statistical significance.

Patients who were treated with high dose vancomycin (≥2 g/day for a mean of 10 ± 2.5 days) had a trend to have recurrences less frequently than the comparison group (Table 2) \( (p = 0.09) \).

Within the group of patients treated with metronidazole, there were no significant differences in the recurrence frequency by the type of metronidazole regimen given \( (X^2 = 3.65, p = 0.45) \). Patients treated with low dose metronidazole (<1 g/day for a mean of 11 ± 8 days) did have a trend \( (p = 0.09) \) for a lower frequency of recurrences (44.8%) than that for those treated with medium dose vancomycin (Table 2). There was no significant reduction in recurrences if patients were treated with either medium dose metronidazole (1.5 g/day for 13 ± 5 days), as 40% recurred \( (p = 0.24) \), or high dose metronidazole (2 g/day for a mean of 16 days), as 0% recurred, but the number of patients treated with high dose metronidazole \( (n = 2) \) had insufficient power to detect a statistical difference. The number of patients treated with tapered doses or pulsed dose regimens of metronidazole was also too low to reach a statistically significant difference \( (n = 2) \).

### Table 3. Description of Vancomycin Taper and Pulsed Antibiotic Regimens

<table>
<thead>
<tr>
<th>Taper (beginning dose to ending dose)</th>
<th>Recurrence (n = 9)</th>
<th>Cure (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>500–125</td>
<td>1 (20%)</td>
<td>4</td>
</tr>
<tr>
<td>750–375</td>
<td>1 (50%)</td>
<td>1</td>
</tr>
<tr>
<td>1000–125</td>
<td>2 (22%)</td>
<td>7</td>
</tr>
<tr>
<td>2000–250</td>
<td>5 (42%)</td>
<td>7</td>
</tr>
<tr>
<td>3000–750</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Total tapered</td>
<td>9 (31%)</td>
<td>20</td>
</tr>
<tr>
<td>Mean days of taper</td>
<td>25.4 ± 13.3</td>
<td>19.5 ± 8.0</td>
</tr>
<tr>
<td>No. of tapers followed by pulses</td>
<td>2 (20%)</td>
<td>8</td>
</tr>
<tr>
<td>Mean days of pulses</td>
<td>3.0 ± 0</td>
<td>6 ± 4.2</td>
</tr>
<tr>
<td>Pulse only</td>
<td>n = 1</td>
<td>n = 6</td>
</tr>
<tr>
<td>500-mg pulse</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>250-mg pulse</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>125-mg pulse</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total pulsed only</td>
<td>1 (14.3%)</td>
<td>6</td>
</tr>
<tr>
<td>Mean days pulsed</td>
<td>9 ± 0</td>
<td>20.3 ± 11</td>
</tr>
</tbody>
</table>

* Recurrence vs cure.

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**Figure 1.** Treatment response in 163 patients with RCDD. 1 = medium dose vancomycin; 2 = low dose vancomycin; 3 = high dose vancomycin; 4 = tapered vancomycin; 5 = pulsed vancomycin; 6 = low dose metronidazole; 7 = medium dose metronidazole; 8 = high dose metronidazole; 9 = miscellaneous. *0.05 < \( p < 0.1 \), compared to medium dose vancomycin (1 g/day); **\( p < 0.05 \), compared to medium dose vancomycin (1 g/day).
end of vancomycin treatment was also associated with a higher recurrence rate. The vancomycin treatment with the highest recurrence rate (medium dose vancomycin) also had the highest persistence of *C. difficile* at the end of vancomycin (27.3%), compared to low dose vancomycin (9%), high dose vancomycin (10%), or vancomycin taper (7.7%) ($r^2 = 0.66$.). Clearance of *C. difficile* was also associated with a lower frequency of recurrences in patients treated with metronidazole ($r^2 = 0.95$). Patients with the highest recurrence rate (low dose metronidazole) had the highest frequency of *C. difficile* persistence (39.3%). Patients with the intermediate recurrence frequency (40%) did not clear *C. difficile* in 33% of cases, and those patients with no recurrences (high dose metronidazole) completely cleared *C. difficile* by the end of therapy.

**DISCUSSION**

RCDD is a difficult clinical problem, as those individuals who have had one recurrence are much more likely to have repeated recurrences. The cycle of recurrences can last for months and even years, resulting in significant disability, loss of income, high medical costs, and the depression and isolation associated with chronic diarrhea. No single treatment approach works for everyone, as witnessed by the various treatment approaches described in the literature. Generally, antibiotic therapy must be repeated, with either metronidazole or vancomycin. However, even the efficacy of these standard treatments has not been well studied in patients with RCDD. Although metronidazole is the recommended first treatment choice for patients experiencing their first episodes of CDD, patients who develop the recurrent form of CDD are usually given vancomycin (1, 15, 22). As evidenced by the data in this study, most patients with RCDD were given vancomycin.

Evidence to support the equal efficacies of vancomycin and metronidazole has been based on older studies of patients randomized to vancomycin or metronidazole who had initial cases of CDD, with some RCDD cases mixed in, but the frequency of recurrent cases was not reported (23–27). The most frequently cited evidence for the equal effectiveness of metronidazole and vancomycin comes from an older study of patients with CDD (23). Of 51 patients randomized to vancomycin (2 g/day), 12% relapsed, *versus* the 39 patients randomized to metronidazole (1 g/day), of whom 5% relapsed ($p = 0.17$).

There have been very few studies in patients with RCDD, and those studies have been very small. Buggy et al. (28) treated seven patients with vancomycin and rifampin and one had a recurrence, but no comparison group was used. Tedesco et al. (29) compared 22 patients with relapsing CDD given 21 days of a tapering dose of vancomycin or a pulsed dose (21 days) of vancomycin and did not document any relapses during follow-up, which varied from 2 to 12 months. Other antibiotics have been used, including rifampin and bacitracin. Wenisch et al. (30) compared four

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**Figure 2.** Persistence of *C. difficile* in patients with RCDD by the end of antibiotic therapy. *p < 0.01 for patients treated with vancomycin compared to metronidazole.
Other treatments have included binding resins like cholestyramine. Although putatively binding the *C. difficile* toxin, this has not been shown in *vivo*: more likely cholestyramine is helpful because of its nonspecific constipating effect. Efforts at repopulating the altered fecal flora have included use of nontoxicogenic strains of *C. difficile*, but only in two cases (31); other bacteriotherapy using fecal enemas (32, 33); whole gut lavage (34); and stool administered via colonoscope after whole gut lavage (35). Biotherapeutic agents and probiotics have also been used—specifically, the nonpathogenic yeast *S. boulardii* and *Lactobacillus GG*—usually as an adjunct to antibiotic therapy (20).

In this study of RCDD patients, the successes of the two standard antibiotic choices were compared. The antibiotic dose did make a difference, as recurrence rates were lowest with high dose vancomycin, relative to medium or low dose vancomycin. Regimens with tapering or pulsing doses of vancomycin had even lower recurrence rates. Vancomycin was more effective than metronidazole for patients with RCDD. There were not enough cases of pulsed or tapered metronidazole to draw any conclusions.

To determine whether clearance of *C. difficile* by the antibiotic explained this difference in efficacy, we analyzed *C. difficile* from stool samples at the end of antibiotic treatment. Vancomycin was more effective in eliminating *C. difficile* (only 11% were positive, compared to 41% with metronidazole). Similarly, high dose vancomycin was more effective than lower doses in clearing *C. difficile*. *C. difficile* is well known to persist in the stools of patients irrespective of the treatment antibiotic, but attempts to correlate the continued presence of *C. difficile* vegetative cells or toxins with risk for relapse have suffered from the small numbers of patients involved in the studies (23, 30, 36, 37). Bartlett et al. (38) found that six of seven patients who relapsed after vancomycin treatment were positive for toxin B at the conclusion of therapy, versus five of 35 positive in those patients who did not relapse. Fekety et al. (27) reported that 10 of 19 vancomycin-treated patients were culture positive during recovery. Of the positive, five relapsed, whereas no culture negative patients relapsed. In a study of 15 patients with initial CDD (37), all eight patients who relapsed after vancomycin therapy had *C. difficile* in their stools at the end of therapy, but none of those who were cured were positive for *C. difficile*.

Thus it appears that decreasing the load of *C. difficile* in the colon is an important part of breaking the cycle of recurrences. Although both antibiotics effectively eliminated vegetative cells of *C. difficile* (93–96%) by the end of therapy, only vancomycin was effective in clearing *C. difficile* toxins (94%). Even if vegetative cells and toxins were cleared, neither antibiotic was effective in ridding the intestines of the spores of *C. difficile*. These spores are the crux of the problem for patients with RCDD, as they are extremely durable and survive in the environment for years. Failure to eliminate *C. difficile* spores has been suggested as a risk factor for CDD, but the present study is the only investigation addressing this point in a sizable patient population (7). Tedesco (29) postulated that recurrences might also be due to persistent spores, possibly in colon diverticula. One hypothesis for the low recurrence rate seen when pulsed doses of vancomycin are given over an extended time (usually 3 wk) is that this type of treatment allows the gradual weeding out of *C. difficile* spores from the intestinal reservoir. The repetitive cycle of antibiotic-free periods (allowing spores to germinate) and pulses of antibiotics (which kills off the newly germinated vegetative cells) may be an effective tactic for treating RCDD. Also, with allowance of antibiotic-free periods, the normal colonic flora has a chance to recolonize. A host defense mechanism of the normal flora is called colonization resistance, or the ability to inhibit the overgrowth of pathogenic organisms (22, 39, 40). Yet we still do not know which bacterial species are responsible for colonization resistance, nor are all the species constituting “normal” flora known (40). In addition, the role of gut immunity seems to play a role in CDD, but this area also needs further study (41).

The advantages of this study are that there are a large number of patients with RCDD who were studied and that there was consistency in the follow-up. However, because the randomization in the original studies was to an investigational biological or a placebo, the different antibiotic treatments were not controlled or randomized. To conclusively prove the most effective antibiotic therapy for patients with RCDD, an additional study that would randomize patients to different antibiotic treatments and has a defined control group should be done.

In summary, we find that pulsing and/or tapering doses of vancomycin were the most effective in breaking the cycle of *C. difficile* recurrences in this case cohort. Short courses of antibiotics may not adequately clear *C. difficile* effectively to reduce the risk of further recurrences. Longer courses using tapered or pulsed doses of vancomycin may act as a buffer, allowing the time needed to both clear *C. difficile* from the intestines and allow restoration of the normal intestinal microflora. Whatever treatment is used for patients with RCDD, some type of buffer (either pulsed antibiotics or biotherapeutic agents) seems to be required to allow time for the colonic flora to recover. A better understanding of complex interactions of the colonic microecology may result in better treatment strategies.

ACKNOWLEDGMENT

This study was supported by Laboratoires Biocodex, France.

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REFERENCES