Recurrent *Clostridium difficile* Diarrhea: Characteristics of and Risk Factors for Patients Enrolled in a Prospective, Randomized, Double-Blinded Trial


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Recurrence of *Clostridium difficile* diarrhea (RCDD) occurs in 20% of patients after they have received standard antibiotic treatment with vancomycin or metronidazole, but the reasons for the recurrences are largely unknown. Patients receiving vancomycin or metronidazole for active *C. difficile* diarrhea (CDD) were referred to our study centers for treatment and a 2-month follow-up as part of a randomized placebo-controlled trial. Sixty patients had RCDD (median number of episodes, 3.0; range, 2–9 episodes) and 64 were having their first episode of CDD. Patients with RCDD had more-severe abdominal pain and were more likely to have fever but initially responded well to antibiotic therapy. Data on sequential episodes showed no progression in disease severity. Five factors were associated with a higher risk of RCDD: the number of previous CDD episodes, onset of the initial disease in the spring, exposure to additional antibiotics for treatment of other infections, infection with immunoblot type 1 or 2 strains of *C. difficile*, and female gender. These factors may help to identify patients who are more likely to develop RCDD and require careful medical supervision.

*Clostridium difficile* is the most frequent nosocomial gastrointestinal pathogen isolated from hospitalized adults, and it has also become a problem for outpatients and patients in extended-care facilities [1–7]. *C. difficile* disease usually occurs following use of antibiotics, may be fatal, and may present as mild diarrhea, nonspecific colitis, pseudomembranous colitis (PMC), toxic megacolon, or colonic perforation [8–9]. Recent studies of *C. difficile* diarrhea (CDD) have focused on diagnostic methods, nosocomial transmission, and treatment strategies [1, 4, 7, 10, 11]. Relatively little attention has been given to patients who have recurrent episodes of CDD. Most patients develop recurrences within the first 2 months after receiving oral therapy with vancomycin or metronidazole for CDD [1, 4]. The reported rate of recurrence has varied from 5% to 66%; however, a rate of 20% has been cited as the mean rate of recurrence after therapy with either vancomycin or metronidazole has been administered [8–16]. At present there is no method to predict which patients will develop recurrences, although recurrences are commonly thought to occur because of poorly understood factors that result in decreased intestinal flora resistance to colonization with *C. difficile* [1, 10]. The objectives of the present study were to use data from patients enrolled in a treatment trial, to compare patients with a history of recurrent CDD (RCDD) with those who were having their first episode of CDD in order to determine how RCDD differs clinically from the initial episode of CDD, and to prospectively identify risk factors for RCDD during the 2 months after the enrollment episode.

Materials and Methods

Patients and follow-up. Adult patients with active CDD who were receiving standard treatment with oral vancomycin or oral metronidazole were screened and interviewed. Patients were eligible for enrollment in the study if they were >17 years of age, had a positive *C. difficile* stool assay (culture or toxin assay), and were having an acute episode of CDD. Patients were excluded from the study if they had had chronic diarrhea prior to the CDD episode; if they had AIDS, immunosuppression due to cancer chemotherapy (administered within the previous 3 months), allergy to vancomycin and metronidazole, or a negative *C. difficile* stool assay (culture or toxin assay).
mild diarrhea, nonspecific colitis (i.e., endoscopic evidence of
that has been previously described [18].

typed in a blinded manner by means of an immunoblot method
bowel habits (at least three loose or watery bowel movements
metronidazole), was effective in preventing further recurrences
but was not prohibited. Stool samples were collected at the end
of each patient’s physician) was initiated.

Use of other antidiarrheal therapies (e.g., loperamide or diphe-
nyloxylic acid hydrochloride) during the study period was to be avoided
but was not prohibited. Stool samples were collected at the end
of antibiotic treatment and 3–4 weeks after antibiotic treatment
was discontinued; the samples were tested for the presence of
C. difficile (culture and/or toxin assay). Colonoscopy and sigmoid-
scopy were performed at the physician’s discretion.

For 2 months, patients kept a standardized daily diary of the
frequency and consistency of stools and of other symptoms.
Diary information was verified during weekly telephone interviews. Data for this study
were collected as part of a double-blinded, placebo-controlled
clinical trial to evaluate the efficacy of an adjunctive biothera-
peutic agent. The results from this latter trial have been reported
and were collected as part of a double-blinded, placebo-controlled
clinical trial to evaluate the efficacy of an adjunctive biothera-
peutic agent. The results from this latter trial have been reported

Case definitions. CDD was defined on the basis of all three
of the following criteria: (1) at least one positive standard
C. difficile assay (culture or toxin A or B assay), (2) the pres-
ence of antibiotic-associated diarrhea, defined as a change in
bowel habits (at least three loose or watery bowel movements
per day for at least 2 consecutive days) following exposure to
antibiotics; and (3) the exclusion of other etiologies of diarrheaa
[1]. Initial CDD was defined as patients enrolled during the
first episode of CDD; RCDD was defined as patients enrolled
after at least one prior episode of CDD. Standard culture proce-
dures and commercial kits for toxin A and toxin B tissue-
culture assays were used [11, 17]. C. difficile isolates were

colitis in the absence of pseudomembranes or diarrhea with
fecal WBCs and abdominal symptoms when no endoscopic
examination was done), or PMC that was diagnosed at endo-
scopy. Antibiotic treatment failure was defined as diarrhea that
did not resolve by the end of a 7–10-day course of standard
oral antibiotic therapy. A prospective recurrence of CDD was
defined as a new episode of CDD (as defined above) that
occurred after resolution of the enrollment episode but before
the end of the 2-month follow-up period.

For analysis of seasonal trends, each season consisted of 3
months, with winter beginning in December.

Statistical methods. All 124 enrolled patients (60 with
RCDD and 64 with initial CDD) were included in a retrospec-
tive analysis of clinical and diagnostic characteristics of the
enrollment episode of CDD. Data collected at enrollment from
interviews and medical records were used for this analysis. For
analysis of prospective risk factors for recurrences, only the
data gathered during the 2-month follow-up of the 67 patients
assigned to placebo in the published double-blind study were
used. This procedure was necessary because S. boulardii was
found to prevent further CDD recurrences, and inclusion of the
patients who received S. boulardii might have biased the results

Mean differences between groups of normal distributions
were assessed with use of Student’s t test. For nonparametric
data, differences in medians were assessed by the Mann-Whit-
ney U test. Differences between categorical variables were
assessed with the χ² statistic (or Fisher’s exact test if the sample
size was small). Two-tailed tests of significance were used for
all tests at P ≤ .05. For the prospective evaluation of multiple
risk factors for the recurrent CDD, adjusted odds ratios were
calculated from logistic regression models [19].

Regression variables were fitted by a forward step-wise
approach with use of EGRET software (Statistics & Epidemiol-
yology Research Corporation, Seattle). Coefficients of the regres-
sion variables were tested for significance by using differences
of log likelihood statistics interpreted as χ². Confidence inter-
vals were calculated from the maximum likelihood estimates
of the standard errors derived from the logistic models.

Results of the Retrospective Analysis

Prior episodes. Of the 124 patients enrolled with active
CDD, 60 (48%) had a history of one or more CDD episodes
and were considered to have RCDD, while 64 (52%) were
having an initial episode. Patients with RCDD reported a me-
dian of 3.0 (range, 1–9) prior episodes at enrollment.

When we examined the time between the first episode of
CDD and the recurrent episode of CDD, the chronic nature of
RCDD became apparent. Patients with RCDD reported that
their disease began (time of the initial episode) a median of
129 days (range, 20 days–4.3 years) before enrollment, while
patients with initial CDD reported that the episode began a
median of 9 days before enrollment (U [Mann-Whitney rank
Table 1. Characteristics of patients with recurrent *Clostridium difficile* diarrhea (CDD) or an initial episode of CDD.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) with recurrent CDD (n = 60)*</th>
<th>No. (%) with initial CDD (n = 64)*</th>
<th>Statistical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral temperature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 37.8°C</td>
<td>26 (43)</td>
<td>8 (13)</td>
<td>$\chi^2 = 13.8; df = 1$</td>
</tr>
<tr>
<td>&lt; 37.8°C</td>
<td>32 (57)</td>
<td>55 (87)</td>
<td>$P &lt; .001$</td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>50 (83)</td>
<td>20 (32)</td>
<td>$\chi^2 = 30.5; df = 1$</td>
</tr>
<tr>
<td>Absent</td>
<td>10 (17)</td>
<td>42 (68)</td>
<td>$P &lt; .001$</td>
</tr>
<tr>
<td>Severity of CDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>18 (30)</td>
<td>11 (17)</td>
<td>$\chi^2 = 4.99$</td>
</tr>
<tr>
<td>Colitis</td>
<td>18 (30)</td>
<td>15 (23)</td>
<td>$df = 2$</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (40)</td>
<td>38 (59)</td>
<td>$P = .08$</td>
</tr>
<tr>
<td>Mean age (y) ± SD</td>
<td>58.6 ± 16.5</td>
<td>57.6 ± 24.3</td>
<td>$t = 0.27; P = NS$</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51 (85)</td>
<td>44 (69)</td>
<td>$\chi^2 = 3.7; df = 1$</td>
</tr>
<tr>
<td>Male</td>
<td>9 (15)</td>
<td>20 (31)</td>
<td>$P = .05$</td>
</tr>
<tr>
<td>Mean no. of concomitant acute medical conditions ± SD</td>
<td>1.9 ± 2.2</td>
<td>2.8 ± 2.1</td>
<td>$t = 2.1; P = .04$</td>
</tr>
<tr>
<td>Mean no. who had undergone prior surgery ± SD</td>
<td>1.1 ± 1.6</td>
<td>1.0 ± 1.6</td>
<td>$t = 0.3; P = NS$</td>
</tr>
</tbody>
</table>

NOTE. NS = not significant; * = $t$ method.

* Numbers are no. (%) unless otherwise indicated.

sum statistic] = 1,324; $P < .01$). The median interval between the beginning of the current CDD episode and time of enrollment was similar for patients with RCDD (14 days) and those with initial CDD (9 days); this finding indicates that the time that medical therapy was initiated was similar regardless of the patient’s history.

**Clinical characteristics.** We compared the symptoms and demographic characteristics of patients with RCDD and of those with initial CDD (table 1). The frequency of abdominal complaints, such as cramping or pain from the enrollment episode, was higher among patients with RCDD than among those with initial CDD (83% vs. 32%, respectively), but the frequencies of other symptoms such as nausea and vomiting was not higher among patients with RCDD. Patients with RCDD also had fever more often than did patients with initial CDD (43% vs. 13%, respectively). At enrollment, the frequency of colitis (nonspecific colitis or PMC) was higher among patients with RCDD than among patients enrolled with initial CDD (60% vs. 41%, respectively; $\chi^2 = 3.9; df = 1$; $P = .05$). There were no statistically significant differences between patients with RCDD and those with initial CDD, as judged by mean daily stool frequency (2.9 ± 1.9 and 2.3 ± 1.2, respectively; $t = 1.97; P = .05$) or duration of the enrollment episode of CDD (19 ± 39 days and 19 ± 16 days, respectively; $t = 0.07; P = .94$).

With respect to demographic characteristics, patients with RCDD were significantly more often female than male (51 [85%] of 60 patients) than were patients with initial CDD (44 [69%] of 64 patients), but the age distribution was similar in both groups (table 1). The mean number (±SD) of concomitant active medical conditions at enrollment was higher for patients with initial CDD (2.8 ± 2.1 concomitant conditions) than among those with RCDD (1.9 ± 2.2 concomitant conditions; $P = .04$), but there were no other statistically significant differences in terms of the number of recent surgeries, allergies, or other medications administered.

The question of whether RCDD is a progressive disease was examined on the basis of data gathered from sequential episodes. For patients with RCDD, the severity of CDD (as measured by stool frequency, abdominal cramping, fever, or time between episodes) did not appear to become progressively worse as the numbers of episodes increased (table 2). However, the risk of having another recurrence of CDD was proportional to the number of previous episodes ($\chi^2 = 19.1; P = .01$).

**Diagnosis of RCDD.** Differences in diagnostic methods were observed for patients with RCDD and those with initial CDD (table 3). Diagnosis of the first episode of initial CDD was usually based on the results of both stool culture and a toxin assay. In contrast, diagnoses of recurrences were more often based only on a toxin assay (78% of RCDD episodes vs. 58% of initial CDD episodes).

One patient’s episode was diagnosed on the basis of a positive *C. difficile* culture alone, but pseudomembranes were observed in this patient during sigmoidoscopy. One patient’s recurrence of PMC was not diagnosed based on the results of enrollment *C. difficile* assays, but this patient had a history of...
positivity for toxin B and also had pseudomembranes that were seen during sigmoidoscopy. Patients with RCDD were more likely to undergo endoscopic examination than were patients with initial CDD (62% vs. 33%, respectively; \( P = .002 \)). Episodes of RCDD could not be distinguished from episodes of initial CDD on the basis of the frequency with which fecal leukocytes were detected in stained smears of diarrheal stools (\( P = .83 \)).

**Incitant antibiotics.** The type of antibiotic therapy that preceded the first episode of CDD was not significantly different for patients with RCDD and those with initial CDD (\( \chi^2 = 2.7; \ P = .44; \) data not shown). Of the 105 patients reporting use of a specific type of antibiotic, nearly two-thirds (\( n = 66 \)) of the patients reported that a single antibiotic was associated with the development of CDD, while 39 (37%) reported that they had received multiple incitant antibiotics; the specific antibiotic was unknown for 19 patients. Of the 175 types of antibiotics documented, the most frequently used were cephalosporins (61 of 175, 35%) or penicillins (47 of 175, 27%). The most frequently implicated cephalosporin was cefuroxime (10 of 61 patients [16%]), and the most frequently implicated penicillin was amoxicillin/clavulanate (14 of 47 patients [30%]). Data on the dosage or duration of the incitant antibiotic therapy were not collected consistently and, therefore, not analyzed.

**Antibiotic treatment.** Statistically significant differences were observed with regard to the type of antibiotic given for treatment of the enrollment episode in patients with initial CDD vs. those with RCDD (\( \chi^2 = 16.9; \ df = 2; \ P < .001 \)). For patients with initial CDD, vancomycin alone or metronidazole alone had been given with equal frequency (41% of patients) or used sequentially (19%) when one was ineffective or adverse reactions developed. In contrast, when a patient with RCDD

### Table 2. Clinical severity of *Clostridium difficile* diarrhea, by sequential episodes.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>History of prior episodes of CDD</th>
<th>Time between episodes (median no. of d)</th>
<th>Stool frequency (median no. per d)</th>
<th>Percentage with abdominal pain</th>
<th>Percentage with fever</th>
<th>Probability of a new recurrence of CDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>64</td>
<td>—</td>
<td>8.5</td>
<td>32</td>
<td>13</td>
<td>0.24</td>
</tr>
<tr>
<td>1</td>
<td>11</td>
<td>34</td>
<td>8.0</td>
<td>87</td>
<td>52</td>
<td>0.71</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>34</td>
<td>6.0</td>
<td>79</td>
<td>33</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>27</td>
<td>6.0</td>
<td>79</td>
<td>41</td>
<td>0.50</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>65</td>
<td>8.0</td>
<td>82</td>
<td>37</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>61</td>
<td>10.0</td>
<td>90</td>
<td>50</td>
<td>0.67</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>57</td>
<td>10.0</td>
<td>75</td>
<td>75</td>
<td>1.00</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>44</td>
<td>10.0</td>
<td>100</td>
<td>50</td>
<td>1.00</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**NOTE.** NA = data not available.

### Table 3. Comparison of the methods for diagnosing recurrent *Clostridium difficile* diarrhea vs. initial *C. difficile* diarrhea.

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>No. (%) with RCDD (n = 60)</th>
<th>No. (%) with initial CDD (n = 64)</th>
<th>Statistical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection of <em>C. difficile</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture alone</td>
<td>0</td>
<td>1 (1)*</td>
<td>( \chi^2 = 7.1 )</td>
</tr>
<tr>
<td>Toxin assay alone</td>
<td>47 (78)</td>
<td>37 (58)</td>
<td>df = 2</td>
</tr>
<tr>
<td>Both culture and toxin assay</td>
<td>12 (20)</td>
<td>26 (41)</td>
<td>( P = .03 )</td>
</tr>
<tr>
<td>Neither method</td>
<td>[1]</td>
<td>[0]</td>
<td></td>
</tr>
<tr>
<td>Endoscopy(^1)</td>
<td>Performed</td>
<td>37 (61.7)</td>
<td>21 (32.8)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>23 (38.3)</td>
<td>43 (67.2)</td>
</tr>
<tr>
<td>Detection of fecal WBCs</td>
<td>Yes</td>
<td>20 (37.0)</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34 (63.6)</td>
<td>40 (66.7)</td>
</tr>
<tr>
<td></td>
<td>Not performed</td>
<td>[6]</td>
<td>[4]</td>
</tr>
</tbody>
</table>

**NOTE.** RCDD = recurrent *C. difficile* diarrhea. Data shown in brackets not included in statistical analysis.

\(^1\) Diagnosed by sigmoidoscopy only.
was enrolled, vancomycin alone had usually been given (77% of patients), while metronidazole alone (18%) or both antibiotics (5%) had been given less frequently.

In addition, patients with RCDD had previously continued to have recurrences after the following regimens were administered: for all prior episodes, vancomycin alone (11 patients) or metronidazole alone (4); both vancomycin and metronidazole (22); or both antibiotics plus miscellaneous treatments including toxin binders (11), bacitracin (4), rifampin (2), ciprofloxacin (2), Lactobacillus species (2), lincomycin (1), or loperamide (1).

Six patients (4.8%) (four with RCDD and two with initial CDD) continued to have diarrhea throughout the course of treatment with vancomycin or metronidazole for the episode of CDD, and the diarrhea continued for a mean (± SD) of 10.5 ± 4.4 days after cessation of antibiotic therapy; thus, antibiotic treatment was considered to have failed for these patients, and they were not considered to have had recurrences of CDD. C. difficile was not eradicated by the end of antibiotic treatment in one of these six patients.

A review of records revealed the likely reasons for the continuation of diarrhea during treatment in five of the six patients; these reasons included lactose intolerance, an adverse reaction to oral hydroxyurea, chronic diarrhea of unknown etiology, a history of irritable bowel syndrome, and pancreatic insufficiency.

Figure 2. Frequency of immunoblot types of Clostridium difficile isolated from patients with enrollment episodes of recurrent C. difficile diarrhea (CDD) (■) or initial CDD (■).

Figure 1. Season of onset of the first episode of Clostridium difficile diarrhea (CDD) according to the number of patients who developed recurrent CDD (■) and the number of patients who had only one episode of CDD that did not recur (■).

Time of initial onset of disease. We determined the month of onset of the first CDD episode for all patients. When patients with RCDD and those with initial CDD were compared (figure 1), we found that patients whose initial episode started in the summer months were the least likely to develop further recurrences, while patients whose initial episode started in the spring were most likely to develop RCDD ($\chi^2$ for trend = 7.8; $P = .005$). Factors that did not appear to account for this unexpected seasonal trend included age, gender, type of inciting antibiotics prescribed, geographic location, or C. difficile immunoblot type.

C. difficile strain type. In an effort to determine if specific strains of C. difficile were more virulent (as defined by their propensity to cause RCDD) than others, immunoblot typing was done on available isolates. Of 81 patients whose stools were cultured for C. difficile, 39 had a culture positive for C. difficile; 27 (69%) of these isolates were available for immunoblot typing. These isolates belonged to nine strain types (figure 2); 37% of them were closely related strain types (7a and 7b) even though the patients were from disparate geographic areas.

Immunoblot strain types 1 and 2 were associated with a significantly higher frequency of recurrences than were the other strain types (Fisher’s exact test; $P = .03$). There was no correlation between strain type and the severity of CDD. Sequential isolates (one pair of type 1 and two pairs of type
Table 4. Multivariate analysis of the risk factors for developing recurrent *Clostridium difficile* diarrhea.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio*</th>
<th>P value, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Season of onset of RCDD1</td>
<td>7.73</td>
<td>.04, 1.07–55.89</td>
</tr>
<tr>
<td>History of at least two CDD episodes</td>
<td>3.87</td>
<td>.03, 1.12–13.34</td>
</tr>
<tr>
<td>No. of unrelated antibiotics1</td>
<td>2.97</td>
<td>.03, 1.11–7.93</td>
</tr>
</tbody>
</table>

NOTE. CDD = *C. difficile* diarrhea. RCDD = recurrent CDD.
* Adjusted for all other variables in the model.
1 Spring months (March–May) compared with summer months (June–August).
2 Number of antibiotics given for conditions other than CDD during the 2 months after an episode of CDD.

7a) were available from three patients; typing results indicated the same strain was present during the enrollment episode and the recurrent episode.

Results of the Prospective Analysis

Risk factors for RCDD. To prospectively evaluate risk factors for RCDD, a subset of patients was required that would not be influenced by the effect of the study drug used in the clinical trial in which adjunctive treatment with *S. boulardii* was being evaluated [11]. This subset consisted of the 67 patients with initial or recurrent episodes of CDD who were assigned to placebo, treated with standard antibiotic therapy, and followed up for 2 months. To assess for selection bias, we compared the 67-patient subset assigned to placebo with the total 124 patients (receiving either placebo or study drug).

There were no significant differences between the two groups in terms of age, gender, severity and type of CDD, number of prior episodes of CDD, or type of antibiotic treatment. The mean (±SD) age of the 67 patients who received placebo was 59.2 ± 21.1 years; 53 (79%) were female, and 14 (21%) were male.

The severity of CDD was also similar: 38 (57%) had diarrhea, 15 (22%) had colitis, and 14 (21%) had PMC. The number of patients in this subset with RCDD (34 [51%]) and initial CDD (33 [49%]) was also not significantly different from that in the total group (P = .87). The numbers of prior CDD episodes in this subset were as follows: none (33 patients [49%]), one episode (7 [10%]), two episodes (7 [10%]), three episodes (6 [9%]), four episodes (4 [6%]), and five to nine episodes (10 [15%]).

All 67 patients were treated with either vancomycin or metronidazole (usually for 10 days) and followed up for 2 months to detect subsequent recurrences of CDD. Of the 34 patients enrolled with a history of RCDD, 22 (64.7%) had a subsequent recurrence during follow-up, and 12 did not. Of the 33 patients enrolled with initial CDD, significantly fewer (8 [24.2%]) developed a recurrence during follow-up (χ² = 9.5; P = .002).

Most recurrences of CDD occurred within 2 weeks of the discontinuation of therapy with vancomycin or metronidazole (median time, 12 days; range, 1–51 days). There were only four patients (all with RCDD) with more-delayed recurrences (30–50 days after cessation of antibiotic therapy). Patients who developed a recurrence had been treated with vancomycin (24 patients [80%]) for their enrollment episode more often than had patients who did not have a recurrence (19 [51%]; χ² = 4.7; P = .03), but there were no significant differences by dosage or duration of vancomycin therapy.

Multivariate regression analysis revealed three statistically significant and independent risk factors for RCDD (table 4): season of onset of the first episode, number of prior CDD episodes, and exposure to antibiotics given to treat infections other than CDD shortly after completion of therapy. The adjusted odds ratio for developing RCDD after an episode of CDD that began during the spring was 7.7 (95% CI, 1.1–55.9), as compared with that for disease whose onset was in the summer months; fall and winter were intermediate in frequency (OR = 3.87 [1.12–13.3] and OR = 4.55 [0.7–29.5], respectively). The adjusted odds ratio for the second risk factor, a history of multiple CDD episodes, was 3.9 (95% CI, 1.1–13.3). Patients with a new recurrence of diarrhea had significantly more episodes of CDD before enrollment (mean ±SD number of episodes, 2.9 ± 2.7) than did patients who did not have a recurrence of diarrhea (mean ±SD number, 0.8 ± 1.3; t = 3.9; P < .001), and the adjusted odds of recurrence increased by 1.6 (95% CI, 1.2–2.2) for each episode the patient had experienced.

The third risk factor was exposure to antibiotics (other than vancomycin or metronidazole) given for treatment of infections other than CDD that developed during the 2-month study. In the multivariate model, the odds of recurrence increased multiplicatively by 3.0 (95% CI, 1.1–7.9) with each antibiotic other than vancomycin or metronidazole given to the patient. These antibiotics were prescribed for a variety of common infections, including urinary tract infections, pneumonia, skin infections, and sinusitis. Patients with RCDD were exposed to significantly more antibiotics other than vancomycin or metronidazole (mean ±SD number, 0.87 ± 1.2) than were patients who did not have RCDD (mean ±SD number, 0.38 ± 0.72; t = 2.1; P < .05).

The type of antibiotic (e.g., a cephalosporin or penicillin), the number of days of antibiotic therapy, and the type of infection for which the antibiotic was prescribed were not found to be significantly associated with RCDD. There were no significant interactions between any of the risk factors in the model.

Variables that were not significantly associated with RCDD when the above three risk factors were accounted for in the model included age, gender, number of surgical procedures, allergies, number or type of incitant antibiotics, severity of CDD on enrollment, duration of the current episode before enrollment, symptoms and diagnostic findings on enrollment, number of concomitant medical conditions, and mean number or type of medications given during the study.

Continued carriage of *C. difficile* after treatment of an episode was also analyzed as a risk factor for RCDD. Standard
metronidazole, given for the enrollment episode, significantly increased the risk for RCDD.

A chronic disease that may recur over a period of months or years.

### Risk factors
- Directly proportional to the number of previous CDD episodes*
- Highest risk if onset of initial episode occurred in the spring, lowest risk if onset occurred in the summer
- Antibiotic treatment or prophylaxis for another infection shortly after a CDD episode
- Female gender
- Disease caused by immunoblot type 1 or type 2 strain of *Clostridium difficile*
- Post-antibiotic treatment carriage of *C. difficile* is not a risk factor
- No difference in risk by type of antibiotic treatment (vancomycin or metronidazole)

### Other characteristics
- Diarrhea initially resolves with vancomycin or metronidazole therapy but then recurs within 2 weeks of end of therapy
- Most often diagnosed by toxin B (cytotoxin) assay alone
- Endoscopy more frequently performed
- A chronic disease that may recur over a period of months or even years

* *C. difficile* diarrhea, colitis, or pseudomembranous colitis.

### Table 5. Characteristics of recurrent *Clostridium difficile* diarrhea.

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent episodes of diarrhea</td>
</tr>
<tr>
<td>Fever and abdominal cramps (usually)</td>
</tr>
<tr>
<td>Colitis with or without pseudomembranes (common)</td>
</tr>
<tr>
<td>Symptoms of diarrhea (frequency or duration) that are no more severe than those of the initial episode</td>
</tr>
<tr>
<td>Nonprogressive severity of recurrences</td>
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</tbody>
</table>

### Discussion

Patients with RCDD, as compared with those who were effectively cured after their initial episode of CDD, were found to have distinct risk factors and clinical presentations; in addition, the diagnostic methods and therapies were different for these patients (table 5). Risk factors for RCDD differed notably from the reported risk factors for acquisition of *C. difficile* or development of the initial episode of CDD. Risk factors for CDD that have been identified in previous studies include increasing age, female gender, treatment with antibiotics or chemotherapeutic agents, and use of gastrointestinal medications and procedures [3, 20–22]. However, few of these studies indicated whether the episode studied was an initial or a recurrent episode. Previous attempts to uncover risk factors for multiple recurrences of CDD have not been productive [1, 10, 12, 23].

In the present study, five factors were associated with increased risk of developing RCDD: onset of the initial disease during the spring months (the lowest risk was associated with onset in the summer); the number of previous episodes; exposure to antibiotics for the treatment of another type of infection that developed shortly after treatment of an episode of CDD; female gender (to a lesser extent); and disease caused by strains of *C. difficile* in immunoblot groups 1 and 2. Factors that were not significantly associated with RCDD included age, type of incitant antibiotic(s) or antibiotics used for treatment of CDD, previous surgery, types of concurrent medical conditions, and use of nonantibiotic medications.

The seasonal trend in the onset of disease is a tantalizing finding that suggests that there may be factors in the spring that predispose patients to episodes of RCDD and that there may be factors in the summer that prevent these episodes. Bowen et al. [24] noted an increase in the recovery of *C. difficile* isolates from December to February during a 2-year surveillance study at a university hospital in Kentucky; seasonal variations have not been reported in most other surveillance studies [4, 7]; in addition, strain types or other differences have not been examined.

The seasonal trend observed in the present study was not evident until patients with RCDD or initial CDD were stratified and then compared; this circumstance may explain why this seasonal trend has not been found in previous studies. Although the factors examined (such as type of incitant antibiotic, *C. difficile* immunoblot type, geographic locale, or age) could not explain the seasonal trend, further investigation is needed to determine if seasonal risk factors for RCDD exist, especially if seasonal differences exist with respect to the use of antibiotics (e.g., more prescriptions for antibiotics, use of higher-risk types of antibiotics, repeated regimens).

The second risk factor (i.e., the number of previous episodes of CDD) was associated with a striking increase in the odds of developing RCDD, and this association has not been examined in previous studies [2, 10, 20, 23]. The finding that the number of previous episodes greatly increases the risk of subse-
quent recurrences may be due to both environmental and host factors. Environmental contamination with the spores of *C. difficile* has been well documented, and these spores have been shown to remain viable for up to 5 months on environmental surfaces [2, 3, 25, 26]. Patients who have had prior episodes probably have contaminated their homes with spores and might become reinfected after antibiotic therapy for an episode is discontinued.

Another explanation for repeated episodes of CDD may be endogenous carriage of *C. difficile* that was not eradicated during antibiotic therapy. In the present study, carriage of *C. difficile* in stools within 72 hours after antibiotic therapy had been discontinued was not a reliable predictor of another recurrence of CDD, but the presence of *C. difficile* 2–3 weeks after antibiotic therapy had been discontinued was a predictor of a subsequent recurrence.

Several groups of investigators have examined the persistence of *C. difficile* at the end of standard antibiotic treatment; in three studies, a positive association between persistence of the organism and recurrence of CDD was observed [14, 16, 27], while no association was observed in another study [23]. Immunoblot typing was done for three patients from whom paired samples (i.e., an isolate from the enrollment episode and another isolate from the recurrent episode) were available. All pairs of isolates were of the same strain, which may indicate endogenous persistence of the organism in the patients' colons or reacquisition of the original strain from exogenous environmental sources contaminated with spores. Several studies have indicated that ~50% of patients have recurrent episodes due to the strain that caused the initial episode, while 50% have recurrences due to a new strain [28–30].

The third risk factor we identified was exposure to antibiotics for treatment of another type of infection within the 2 months after onset of the enrollment episode of CDD; with each antibiotic prescribed, this risk factor was associated with an incremental increase by a factor of 3.0 in the odds of developing RCDD.

Silva et al. [31] found that two (12.5%) of 16 patients treated for CDD who were given another antibiotic developed a recurrence [31]. These observations seem logical when the generally accepted theory of the pathogenesis of CDD is taken into consideration. Normal colonic flora is believed to produce a protective “colonization resistance” barrier to *C. difficile*, and factors such as use of antibiotics or gastrointestinal procedures or medications are known both to disrupt this barrier and to be risk factors for the development of CDD [2, 10, 20, 21, 32]. Cephalosporins, penicillins, and clindamycin have been implicated most commonly in the induction of CDD; however, nearly all types of antibiotics have been implicated [1, 10].

The exposure to additional antibiotics that suppress the protective colonic flora may easily lead to further recurrences of CDD. In addition, antibiotics (including vancomycin or metronidazole) may have little effect on *C. difficile* in the colon because of sporulation or the presence of antibiotic resistance genes commonly carried by the organism [33].

There may be other host factors that increase the risk of developing RCDD. The role of the systemic immune system response has been investigated in a few studies, and lower levels of serum IgG and IgA antibodies to *C. difficile* or its toxins have been found in patients with symptomatic CDD [34, 35]. Since no serum was collected from patients in the present study, this factor could not be analyzed. One patient with recurrent CDD and selective serum IgG1 deficiency had no further recurrences when treated with a combination of intravenous immune globulin, vancomycin, and *S. boulardii* [36].

RCDD was found to be a more severe disease than initial CDD, but fortunately, the severity of RCDD did not seem to progress as the number of episodes increased. RCDD can be a prolonged and chronic illness; in fact, one of our patients had intermittent CDD for 4.3 years. Most recurrences observed in our study occurred within 1–2 months after antibiotic therapy was discontinued; this observation has been noted in previously published studies [1, 10, 14, 27]. However, the time between episodes varies widely; thus, we may have missed some episodes that occurred after the 2-month follow-up period.

The methods of diagnosis were often different for episodes of RCDD and episodes of initial CDD. Patients with RCDD were more likely to undergo diagnostic colonoscopy or sigmoidoscopy, which probably reflects the tendency to treat initial episodes presumptively and to reserve invasive procedures for recurrences when there is more concern about the accuracy of the diagnosis. As was reported in another study, the presence of fecal leukocytes did not appear to be a factor in the differentiation between an episode of RCDD and an episode of initial CDD [37].

The most effective treatment for CDD has been debated in the literature. Suggested therapies include no antibiotic treatment for mild diarrhea, specific oral antibiotics, biotherapeutic agents, fecal enemas, and antibiotic enemas [1, 38–40]. Because of our study design, we could not compare patients who received no antibiotics with those who received therapy for CDD. When the illness is not severe, some authorities advise against specific therapy because some studies have indicated that this approach may result in fewer relapses. The results of our study showed that the initial symptomatic response to either vancomycin or metronidazole was excellent in that only 4.8% of patients failed to respond to treatment given for ≤10 days. This response rate is similar to the 2% failure rate found in a 10-year surveillance study [4].

Similar findings were reported in an earlier study involving 46 patients, four of whom required treatment for >10 days because they responded slowly to vancomycin therapy [16]. Two of these four patients had underlying chronic inflammatory bowel diseases, and one had diabetes mellitus and a history of chronic diarrhea. The results of these studies suggest that patients with preexisting, usually mild intestinal disorders that are associated with diarrhea may have a slow or delayed response to therapy with vancomycin or metronidazole. Thus, in
situations where there are two concurrent possible etiologies of diarrhea, the true response to treatment may be difficult to judge.

Once a patient has responded to antibiotic therapy and symptoms cease, CDD may recur after antibiotic treatment is discontinued. Recurrence rates after treatment with vancomycin have ranged from 6% to 66% [13, 16, 27, 28], whereas recurrence rates after treatment with metronidazole have ranged from 27% to 42% [9, 15]. Olson et al. [4] reported that 6% of patients treated with oral metronidazole and 10% of patients treated with oral vancomycin relapsed; however, because of the definition of relapse in their study, patients exposed to additional antibiotics were excluded [4]. In a prospective study, Wenisch et al. [40] found that although 94% of the patients initially responded to antibiotic therapy, clinical symptoms recurred in 16% whether they were treated with vancomycin or metronidazole [40].

Few investigators have compared recurrence rates that are stratified according to a history of CDD, and this may be one reason why the reported recurrence rates have varied so dramatically. In the present study the recurrence rate was 65% for patients with a history of RCDD and 24% for patients with an initial episode of CDD. The frequency of recurrence was higher for patients treated with vancomycin than for those treated with metronidazole, a finding that was probably due to the fact that vancomycin was given more often to patients with a history of CDD. Since the probability of recurrence is higher for these patients, clinicians should not draw the conclusion that vancomycin is less effective for the treatment of RCDD.

The comparative effectiveness of antibiotic treatment may be most readily judged among a group of patients without these confounding factors. For the 33 patients with an initial episode of CDD (who were treated with antibiotics and placebo), the frequency of recurrence did not differ significantly according to the choice of antibiotic therapy: 18% of patients who received metronidazole alone, 33% who received vancomycin alone, and 43% who received both antibiotics sequentially had recurrences of CDD (χ² = 1.8; P = .4).

It is reassuring that the effectiveness of metronidazole is similar to that of vancomycin for treating RCDD because physicians are now being advised to minimize the use of vancomycin (especially the oral formulation) in the hope of reducing the emergence of vancomycin resistance in pathogens such as enterococci or staphylococci, for which vancomycin is one of the most important therapeutic agents [41, 42].

The treatment of patients with RCDD is often a challenge for physicians, since these patients often have recurrences after therapy with both commonly recommended antibiotics, given either sequentially or simultaneously. Physicians may need to explore alternative treatments such as S. boulardii, lactobacilli species, intravenous IgG, bactracin, rifampin, teicoplanin, or rectal infusions of feces to affect a cure in these patients [11, 36, 40, 43–48].

There are several caveats about the results of the present study. This population of refractory patients is not representative of the majority of patients with a first episode of nosocomially acquired CDD. The patients with RCDD represent a group of patients who are clearly more prone than average to multiple recurrences of CDD. Furthermore, the difficulty in obtaining stool for cultures from referral patients prior to the initiation of therapy limited our ability to analyze the association between strain differences and the development of RCDD, the seasonal occurrence of strain types, and the question of whether recurrences are due to the same strain or to reinfection with a newly acquired strain.

The data from this study indicate that there are two subsets of patients with CDD: one subset responds well to initial therapy with vancomycin or metronidazole, and the other subset is at increased risk of developing RCDD. Patients with RCDD pose a challenge for effective prevention of further recurrences even though their initial response to antibiotic therapy for each episode seems adequate. RCDD may become persistent and elude long-term cure after therapy with either vancomycin or metronidazole.

An important finding from the present study is that exposure to antibiotics given for treatment of other types of infections is a significant risk factor for further recurrences of CDD and that the risk of recurrence increases as the number of antibiotics given increases. Therefore, we believe that physicians should exercise caution when prescribing antibiotics for infections that occur within 1–2 months after an episode of CDD and that physicians should be cognizant of the fact that such antibiotic therapy may trigger further episodes of CDD.

References