Decreased Cure and Increased Recurrence Rates for *Clostridium difficile* Infection Caused by the Epidemic *C. difficile* BI Strain

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**Background.** An epidemic strain of *Clostridium difficile* designated by restriction endonuclease analysis (REA) as group BI has caused multiple outbreaks of severe *C. difficile* infection (CDI). The treatment response of patients infected with this strain is uncertain.

**Methods.** *Clostridium difficile* isolates were collected from 2 phase 3 clinical trials comparing fidaxomicin to vancomycin and typed using REA. Clinical cure and recurrence outcomes were analyzed by strain type of the infecting organism, BI and non-BI, using both univariate and multivariate analyses.

**Results.** From 999 patients, 719 isolates were available for typing (356 fidaxomicin treated and 363 vancomycin treated). BI was the most common REA group (34% of isolates). Patients infected with BI had lower cure rates (86.6%; 214 of 247) than those infected with non-BI strains (94.3%; 445 of 472) (P < .001). The cure rate difference between the BI and non-BI patients was significant for both vancomycin (P = .02) and fidaxomicin (P = .007). BI patients had a recurrence rate of 27.4% (51 of 186), compared with a recurrence rate of 16.6% (66 of 397) in non-BI patients (P = .002). By multivariate analysis, BI infection was statistically significant as a risk factor for reduced cure (odds ratio [OR], 0.48; 95% confidence interval [CI], .27–.85; P = .030) and for increased recurrence (OR, 1.57; 95% CI, 1.01–2.45; P = .046).

**Conclusions.** The clinical cure rate of patients infected with the epidemic BI *C. difficile* strain is lower than the cure rate of those infected with non-BI strains whether treated with fidaxomicin or vancomycin. Similarly, the CDI recurrence rate is increased in patients with the BI strain compared with patients with other *C. difficile* strains.

*Clostridium difficile* infection (CDI) has been increasing in incidence and morbidity throughout Europe and North America [1–4] and has recently surpassed methicillin-resistant *Staphylococcus aureus* infections as the leading cause of hospital-acquired infections in some US hospitals [5]. This increase in frequency and severity is coincident with the spread of a strain of *C. difficile* characterized by increased toxin A and toxin B production, the presence of an additional toxin (binary toxin), and increased resistance to fluoroquinolones [3, 6]. This strain, identified as restriction endonuclease analysis (REA) group BI, North American pulsed field type 1 (NAP1), and polymerase chain reaction (PCR) ribotype 027, was originally identified in the 1980s but was not resistant to the newer fluoroquinolone agents and was not epidemic prior to 2000 [3, 7]. Restriction endonuclease analysis group BI/NAP1 *C. difficile* isolates have been recovered from more than half of the stool samples collected in several recent North American surveys of CDI [1, 3, 8].

Treatment of CDI with oral vancomycin or metronidazole is usually successful; however, recent observational studies have shown a decrease in response to treatment, particularly treatment with metronidazole [9].
High rates of disease recurrence are still seen following treatment with both agents [7]. In response to the increased complications of CDI, decrease in treatment responses, and continued high rates of recurrences, new therapies are being developed. One new therapeutic agent is fidaxomicin, formerly known as OPT-80 or PAR-101 [10]. Two phase 3 treatment trials of the same study design compared the safety and efficacy of fidaxomicin vs vancomycin. Results of the first study, with 548 evaluable subjects with mild to severe CDI, have been reported [11]. In this study, we analyze the combined study population from the 2 trials (999 evaluable subjects in the per-protocol population) and report the treatment outcomes in relation to the REA typing results of the infecting C. difficile strains.

METHODS

Clinical Trial Design

Patients included in this study were enrolled in 2 phase 3 clinical trials (OPT-80-003 and OPT-80-004), comparing the efficacy and safety of fidaxomicin vs vancomycin in the treatment of CDI (NCT00314951 and NCT00468728, www.clinicaltrials.gov). These were prospective, multicenter, double-blind, randomized, parallel-group, noninferiority trials, which were conducted between May 2006 and December 2009. Patients were enrolled at sites in the United States, Canada, and Europe. Enrollment criteria included patients with diarrhea, defined as >3 unformed bowel movements in the 24-hour period prior to randomization, and a positive stool toxin assay for C. difficile toxin A or B within 48 hours of randomization. After informed consent was obtained, subjects were randomized to 10 days of treatment with either fidaxomicin at 200 mg bid with matching doses of placebo or vancomycin at 125 mg 4 times daily. Both study medications and the placebo were overencapsulated to blind study participants from medication identity. During the course of the 10-day treatment, patients were evaluated for clinical cure or failure on a daily basis. Patients assessed as meeting criterion for clinical cure were followed for recurrence on a weekly basis for 28 days after the final dose of study medication [11]. Patients in the second phase 3 trial followed the same protocol as the first phase 3 trial [11].

Culture

Stool samples were collected at time of screening, upon early termination or end of therapy visit for clinical failure patients, and upon treatment visits for recurrence patients. Individual study sites performed toxin testing on the stool samples, which were then frozen and sent to a reference laboratory for culture. Culture of the stool specimens for C. difficile was performed at the R. M. Alden Research Laboratory (Culver City, California) using cycloserine-cefoxitin fructose with taurocholate and horse blood agar in an anaerobic chamber. Susceptibility testing of the isolates was also performed using agar dilution methodology (CLSI M11-A7) [12]. Clostridium difficile was recovered from 719 samples. Clostridium difficile isolates were then frozen at −80°C prior to subsequent analysis.

REA Typing

Restriction endonuclease analysis (REA) typing was performed on the recovered C. difficile isolates at the Microbiology Reference Laboratory at the Edward Hines Jr VA Hospital (Hines, Illinois). Typing was performed using HindIII restriction of total cellular DNA, and the fragments were separated by electrophoresis on a 0.7% agarose gel, as previously described [13]. The resulting HindIII restriction patterns were compared with 9 REA groups that have been implicated in epidemics or outbreaks over the last 25 years (REA groups B, Y, J, K, G, BI, CF, DH, and BK). Patterns showing a 90% similarity index were placed in the same REA group. Any pattern that did not match 1 of the 9 groups was designated as a nonspecific REA group.

Multivariate Analysis

Variables analyzed include REA group, age, CDI severity, CDI history, region, antibiotic history prior to CDI treatment, concomitant antibiotics during treatment period, concomitant antibiotics during treatment or follow-up period, and comorbidity. Concomitant antibiotic classes were those previously published for this study by Mullane et al [14]. Univariate analyses were performed using Pearson’s χ² test of independence between variables and outcome of cure and recurrence. Variables with a 2-tailed P value of <.1 in the univariate analysis were included in the multivariate analysis. Logistic regression was used for all multivariate analyses using the per-protocol population data collected from the combined 003 and 004 phase 3 clinical trials. Multicolinearity of the regression model was addressed by examining the tolerance and variance inflation factor (VIF) for each variable. Low tolerance of close to zero and high VIF of >10 indicate presence of multicolinearity. Analysis of the REA groups (BI vs non-BI) was adjusted for age, recent history of CDI, baseline CDI severity, geography, and exposure to concomitant antibiotics to treat other infections. In a separate analysis, patients with isolates (BI or non-BI) were compared with patients with no isolates to determine if the patients with isolates differed statistically from those without isolates. The chi-square test with 2-tailed P value was used to compare categorical variables.

RESULTS

Of the 999 subjects in the per-protocol population, 719 C. difficile isolates were recovered (356 from the fidaxomicin treatment group and 363 from the vancomycin group). Sixty-four percent (460 of 719) of the isolates belonged to 1 of the 9
rea groups (Table 1). Another 36% (259 of 719) of the isolates were members of other less-common REA groups and were designated as nonspecific REA group. BI was the most frequent REA group identified, accounting for 34% (247 of 719) of the isolates. Patients with no isolates were found to be statistically similar to those with isolates (BI and non-BI) with regard to age, CDI severity, prior history of CDI, antibiotic history prior to CDI treatment, and use of concomitant antibiotics during or after treatment, but they were more likely to reside in the United States (59% vs 39%;  _P_ < .0001) and had more comorbidities (77% vs 66%;  _P_ = .0006) (Supplementary Data).

Treatment of CDI with either vancomycin or fidaxomicin resulted in a 91.0% (909 of 999) cure rate. Patients infected with the non-BI group strains had higher cure rates (94.3%; 445 of 472) than those infected with the BI group strains (86.6%; 214 of 247) ( _P_ < .001) (Table 1). In the non-BI group, vancomycin treatment resulted in a 93.2% (220 of 236) cure rate, and fidaxomicin treatment resulted in a 95.3% (225 of 236) cure rate. In the BI group, vancomycin treatment resulted in an 85.8% (109 of 127) cure rate, and fidaxomicin resulted in an 87.5% (105 of 120) ( _P_ = 0.699) cure rate. The difference in cure rate between the BI group and the non-BI group patients was significant for both vancomycin ( _P_ = 0.02) and fidaxomicin ( _P_ = 0.007) treatment.

The overall recurrence rate was 18.9% (150 of 794) (per-protocol analysis), and vancomycin treatment resulted in a higher recurrence rate (24.6%; 99 of 403) than fidaxomicin treatment (13.0%; 51 of 391) ( _P_ < .001). When analyzed by REA typing groups, the non-BI group had an overall recurrence rate of 16.6% (66 of 397), whereas the BI group had a recurrence rate of 27.4% (51 of 186) ( _P_ = .002). Fidaxomicin resulted in lower recurrence rates than vancomycin among non-BI cases (8.4% [17 of 203] vs 25.3% [49 of 194]; _P_ < .001), but recurrence rates for fidaxomicin and vancomycin were not significantly different among BI cases. The BI recurrence rate was 31.3% (30 of 96) after vancomycin and 23.3% (21 of 90) after fidaxomicin ( _P_ = .23).

Patient demographics and disease characteristics are shown in Table 2 for the fidaxomicin- and vancomycin- treated patients. Patients with isolates (BI plus non-BI) and with no isolates did not differ statistically by treatment agent. Univariate analysis of factors influencing clinical cure and recurrence are shown in Tables 3 and 4. Patients with isolates (BI plus non-BI) and with no isolates did not differ statistically in the cure or recurrence rates.

Multivariate analysis (Table 5) confirmed the lower cure rates in patients in the BI group compared with the non-BI group. There was no difference in the cure rate of patients without isolates compared with the non-BI group. Because individual tolerance values were 0.81–0.95 and VIF was 1.04–1.23, no evidence of multicolinearity was present. After adjusting for age, recent history of CDI, severity of CDI, geography, and exposure to concomitant antibiotics to treat other infections, infection with the BI group strain was associated with a reduced odds ratio (OR) for cure compared with non-BI strains (OR, 0.48; 95% CI, .27–.85; _P_ = .03). Comorbidity (OR, 0.39; 95% CI, .19–.80; _P_ = .01) was also found to be associated with decreased cure. In addition, patients in Canada with BI group strain infection were 2.3-fold more likely to be cured than patients in the United States ( _P_ = .01) and 2.0-fold more likely to be cured than patients in Europe ( _P_ = .009). Patients in Europe had a lower, but not significant, recurrence rate than Canadian patients infected with the BI group strain. Infection with the BI group strain (OR, 1.57; 95% CI, 1.01–2.45; _P_ = .046), a previous episode of CDI within the 3 months prior to enrollment (OR, 1.82; 95% CI, 1.15–2.87; _P_ = .01),

### Table 1. Prevalence of Restriction Endonuclease Analysis Groups and Response to Therapy

<table>
<thead>
<tr>
<th>REA Group</th>
<th>Prevalence of REA Groups, No. (% of Patients in Treatment Group)</th>
<th>Cure Rate, No. (%) of Patients in Treatment Group/REA Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vancomycin (n = 363)</td>
<td>Fidaxomicin (n = 356)</td>
</tr>
<tr>
<td>BI</td>
<td>127 (35.0)</td>
<td>120 (33.7)</td>
</tr>
<tr>
<td>BK</td>
<td>7 (1.9)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>CF</td>
<td>2 (0.6)</td>
<td>5 (1.4)</td>
</tr>
<tr>
<td>DH</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>G</td>
<td>29 (8.0)</td>
<td>25 (7.0)</td>
</tr>
<tr>
<td>J</td>
<td>20 (5.5)</td>
<td>23 (6.5)</td>
</tr>
<tr>
<td>K</td>
<td>11 (3.0)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>L</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Y</td>
<td>35 (9.6)</td>
<td>42 (11.8)</td>
</tr>
<tr>
<td>Nonspecific</td>
<td>129 (35.5)</td>
<td>130 (36.5)</td>
</tr>
<tr>
<td>All non-BI</td>
<td>236 (65.0)</td>
<td>236 (66.3)</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; REA, restriction endonuclease analysis.
Table 2. Patient Demographics and Disease Characteristics at Baseline (Per-Protocol Population, N = 999)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Fidaxomicin (n = 481), No. (%)</th>
<th>Vancomycin (n = 518), No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REA group</td>
<td>BI</td>
<td>120 (25.0)</td>
<td>127 (24.5)</td>
<td>.72a</td>
</tr>
<tr>
<td></td>
<td>Non-BI</td>
<td>236 (49.1)</td>
<td>236 (45.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Isolate</td>
<td>125 (26.0)</td>
<td>155 (29.9)</td>
<td>.17b</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;65</td>
<td>255 (53.0)</td>
<td>265 (51.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>226 (47.0)</td>
<td>253 (48.8)</td>
<td>.56</td>
</tr>
<tr>
<td>CDI severity</td>
<td>Mild</td>
<td>129 (26.8)</td>
<td>160 (30.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>179 (37.2)</td>
<td>162 (31.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>173 (36.0)</td>
<td>196 (37.8)</td>
<td>.12</td>
</tr>
<tr>
<td>CDI history</td>
<td>No prior episode</td>
<td>402 (83.6)</td>
<td>435 (84.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>One prior episodec</td>
<td>79 (16.4)</td>
<td>83 (16.0)</td>
<td>.86</td>
</tr>
<tr>
<td>Region</td>
<td>Canada</td>
<td>185 (38.5)</td>
<td>194 (37.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>85 (17.7)</td>
<td>88 (17.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>211 (43.9)</td>
<td>236 (45.6)</td>
<td>.86</td>
</tr>
<tr>
<td>Antibiotic history prior to CDI treatment</td>
<td>No</td>
<td>95 (19.8)</td>
<td>122 (23.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>386 (80.3)</td>
<td>396 (76.5)</td>
<td>.15</td>
</tr>
<tr>
<td>CA during treatment periodd</td>
<td>No</td>
<td>391 (81.3)</td>
<td>416 (80.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>90 (18.7)</td>
<td>102 (19.7)</td>
<td>.69</td>
</tr>
<tr>
<td>CA during treatment or follow-up periodd</td>
<td>No</td>
<td>349 (72.6)</td>
<td>375 (72.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>132 (27.4)</td>
<td>143 (27.6)</td>
<td>.95</td>
</tr>
<tr>
<td>Comorbiditye</td>
<td>No</td>
<td>145 (30.2)</td>
<td>164 (31.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>336 (69.9)</td>
<td>354 (68.3)</td>
<td>.60</td>
</tr>
</tbody>
</table>

Abbreviations: CA, concomitant antibiotics; CDI, Clostridium difficile infection; REA, restriction endonuclease analysis.

a P value comparing patients with BI isolates and patients with non-BI isolates.

b P value comparing patients with isolates (BI and non-BI) and patients with no isolates.

c Previous CDI episode within 3 months prior to enrollment in study.

d For clinical cure, antibiotic exposure during the 10-day treatment period was considered, and for recurrence, antibiotic exposure at any time was considered.

*Comorbidity includes patients with chronic obstructive pulmonary disease, heart failure or myocardial infarction, methicillin-resistant Staphylococcus aureus, renal insufficiency, or cancer; patients on dialysis; patients with hepatic failure; and patients who use proton pump inhibitors or H2 receptor antagonists.

and exposure to concomitant antibiotics (OR, 1.57; 95% CI, 1.03–2.39; P = .04) were all significant risks for increased recurrence of CDI, whereas treatment with fidaxomicin vs vancomycin significantly reduced recurrence (OR, 0.45; 95% CI, 0.31–0.65; P < .0001).

**DISCUSSION**

Restriction endonuclease analysis group BI (NAP1/027) has become the most frequently isolated C. difficile strain in North America. Reports of its disease severity have been mixed; some studies have shown higher disease severity for BI strains than for other strains but have been unable to dissociate the confounding advanced age variable [14, 15], whereas other small studies have failed to show increased severity entirely [16, 17]. We have addressed CDI severity and age in a multivariate analysis and shown that infection with the BI strain results in decreased cure rates compared with infection with other C. difficile strains after treatment with either vancomycin or fidaxomicin. In multivariate analysis, other significant risk factors for reduced cure included only comorbidity (Table 5). These reduced cure rates may explain in part the perceived greater morbidity and mortality previously reported with CDI caused by BI/NAP1 strains, but unfortunately they suggest that treatment outcome of BI strain infections is not likely to be improved by the availability of fidaxomicin for treatment.

Recurrence rates were also higher among BI strain cases than among non-BI strain cases and were not significantly different following treatment with vancomycin or fidaxomicin. It was recently reported that fidaxomicin significantly reduced CDI recurrence rates compared with vancomycin in the first phase 3 comparative study [11]. When analyzed by REA typing, it was apparent in that study that the major reduction in recurrences was in the non-BI strain group. There was no significant reduction in the recurrence rate of REA group BI strain with fidaxomicin compared with vancomycin. Data presented here from both phase 3 trials confirm these findings, and multivariate analysis showed increased recurrence was associated not only with the REA BI group strain but was also significantly associated with having had a previous episode of
CDI prior to enrollment and to exposure to concomitant antibiotics (Table 5).

Multivariate analysis also demonstrated a marked difference in clinical cure of CDI in Canada vs the United States, with Canadian cure rates 2.3 times higher than US cure rates and 2.0 times higher than European cure rates. Reasons for this geographic difference in cure rates are unclear because all investigators were blinded as to the treatment regimen and to the type of organism infecting the patient. One possibility is that patients were enrolled earlier in their course of disease in Canada, resulting in overall better cure rates; however, we have no data to support that hypothesis. Another possibility is that the BI group strains in Canadian patients are different from those in the United States. There is already evidence that this is the case from REA typing of BI group isolates from Canada; however, there is no evidence that such strains may be less virulent [18]. Further subtyping analysis of the BI group strains in this study from Canada vs the United States is possible but has not yet been performed.

Another factor in multivariate analysis that might affect treatment outcome was concomitant antibiotic use, which trended toward reduced clinical cure and was significantly associated with higher recurrence rate. Patient age (<65 vs ≥65 years) was not significantly associated with decreased cure or increased recurrence (Table 5). As expected, a history of prior CDI within 3 months of enrollment was significantly associated with increased recurrence rate in multivariate analysis.

Although not reported in this study, Goldstein et al [12] have compared the relation of minimum inhibitory concentration (MIC) to successful clinical treatment in the isolates from these patients and showed that there was no correlation between the MICs of baseline isolates and the clinical outcome of C. difficile infection. The MIC90s were generally low for both fidaxomicin and vancomycin. BI isolates had higher MICs, but for the majority of isolates, this was only a 1 dilutional difference that is unlikely to account for decreased cure given the extremely high fecal concentrations of both fidaxomicin and vancomycin.

Advantages of this study include the randomized, blinded, prospective study design, the large number of evaluable patients, the use of 2 highly active treatment agents administered in a consistent manner with uniform clinical outcome and recurrence endpoints, and the ability to do multivariate analysis of additional variables. For the first time, we have shown

### Table 3. Univariate Analysis of Factors Likely to Influence Clinical Cure (Per-Protocol Population, N = 999)

<table>
<thead>
<tr>
<th>Variable Category</th>
<th>No Cure (n = 90), No. (%)</th>
<th>Cure (n = 909), No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REA group BI</td>
<td>33/247 (13.4)</td>
<td>214/247 (86.6)</td>
<td>.0004a</td>
</tr>
<tr>
<td>Non-BI</td>
<td>27/472 (5.7)</td>
<td>445/472 (94.3)</td>
<td></td>
</tr>
<tr>
<td>No isolate</td>
<td>30/280 (10.7)</td>
<td>250/280 (89.3)</td>
<td>.24b</td>
</tr>
<tr>
<td>Age &lt;65</td>
<td>37/520 (7.1)</td>
<td>483/520 (92.9)</td>
<td></td>
</tr>
<tr>
<td>≥65</td>
<td>53/479 (11.1)</td>
<td>426/479 (88.9)</td>
<td>.03</td>
</tr>
<tr>
<td>CDI severity Mild</td>
<td>18/289 (6.2)</td>
<td>271/289 (93.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>35/341 (10.3)</td>
<td>306/341 (89.7)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>37/369 (10.0)</td>
<td>332/369 (90.0)</td>
<td>.15</td>
</tr>
<tr>
<td>CDI history No prior episode</td>
<td>78/837 (9.3)</td>
<td>759/837 (90.7)</td>
<td>.15</td>
</tr>
<tr>
<td>One prior episode</td>
<td>12/162 (7.4)</td>
<td>150/162 (92.6)</td>
<td>.44</td>
</tr>
<tr>
<td>Region Canada</td>
<td>18/379 (4.8)</td>
<td>361/379 (95.3)</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>16/173 (9.3)</td>
<td>157/173 (90.8)</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>56/447 (12.5)</td>
<td>391/447 (87.5)</td>
<td>.0005</td>
</tr>
<tr>
<td>Antibiotic history prior to CDI treatment No</td>
<td>13/217 (6.0)</td>
<td>204/217 (94.0)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77/782 (9.9)</td>
<td>705/782 (90.2)</td>
<td>.08</td>
</tr>
<tr>
<td>CA during treatment periodd No</td>
<td>60/807 (7.4)</td>
<td>747/807 (92.6)</td>
<td>.0004</td>
</tr>
<tr>
<td>Yes</td>
<td>30/192 (15.6)</td>
<td>162/192 (84.4)</td>
<td></td>
</tr>
<tr>
<td>Comorbiditye No</td>
<td>10/309 (3.2)</td>
<td>299/309 (96.8)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80/690 (11.6)</td>
<td>610/690 (88.4)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviations: CA, concomitant antibiotics; CDI, Clostridium difficile infection; REA, restriction endonuclease analysis.

a P value comparing patients with BI isolates and patients with non-BI isolates.

b P value comparing patients with isolates (BI and non-BI) and patients with no isolates.

Previous CDI episode within 3 months prior to enrollment in study.

d For clinical cure, antibiotic exposure during the 10-day treatment period was considered.

e Comorbidity includes patients with chronic obstructive pulmonary disease, heart failure or myocardial infarction, methicillin-resistant Staphylococcus aureus, renal insufficiency, or cancer; patients on dialysis; patients with hepatic failure; and patients who use proton pump inhibitors or H2 receptor antagonists.
Table 4. Univariate Analysis of Factors likely to Influence Recurrence (Per-Protocol Population, N = 999)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>No Recurrence (n = 644), No. (%)</th>
<th>Recurrence (n = 150), No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>REA group</td>
<td>BI</td>
<td>135/186 (72.6)</td>
<td>51/186 (27.4)</td>
<td>.002a</td>
</tr>
<tr>
<td></td>
<td>Non-BI</td>
<td>331/397 (83.4)</td>
<td>66/397 (16.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No isolate</td>
<td>178/211 (84.4)</td>
<td>33/211 (15.6)</td>
<td>.16b</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;65</td>
<td>358/428 (83.6)</td>
<td>70/428 (16.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td>286/366 (78.1)</td>
<td>80/366 (21.9)</td>
<td>.048</td>
</tr>
<tr>
<td>CDI severity</td>
<td>Mild</td>
<td>196/237 (82.7)</td>
<td>41/237 (17.3)</td>
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<tr>
<td></td>
<td>Moderate</td>
<td>216/266 (81.2)</td>
<td>50/266 (18.8)</td>
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<tr>
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<td>Severe</td>
<td>232/291 (79.7)</td>
<td>59/291 (20.3)</td>
<td>.68</td>
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<tr>
<td>CDI history</td>
<td>No prior episode</td>
<td>551/666 (82.7)</td>
<td>115/666 (17.3)</td>
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<tr>
<td></td>
<td>One prior episodeb</td>
<td>93/128 (72.7)</td>
<td>35/128 (27.3)</td>
<td>.008</td>
</tr>
<tr>
<td>Region</td>
<td>Canada</td>
<td>256/330 (77.6)</td>
<td>74/330 (22.4)</td>
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<td></td>
<td>Europe</td>
<td>121/140 (86.4)</td>
<td>19/140 (13.6)</td>
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<td>United States</td>
<td>267/324 (82.4)</td>
<td>57/324 (17.6)</td>
<td>.06</td>
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<tr>
<td>Antibiotic history prior to CDI treatment</td>
<td>No</td>
<td>144/183 (78.7)</td>
<td>39/183 (21.3)</td>
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<tr>
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<td>Yes</td>
<td>500/611 (81.8)</td>
<td>111/611 (18.2)</td>
<td>.34</td>
</tr>
<tr>
<td>CA during treatment or follow-up periodd</td>
<td>No</td>
<td>502/609 (82.4)</td>
<td>107/609 (17.6)</td>
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<td></td>
<td>Yes</td>
<td>142/185 (76.8)</td>
<td>43/185 (23.2)</td>
<td>.08</td>
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<tr>
<td>Comorbiditye</td>
<td>No</td>
<td>225/271 (83.0)</td>
<td>46/271 (17.0)</td>
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<tr>
<td></td>
<td>Yes</td>
<td>419/523 (80.1)</td>
<td>104/523 (19.9)</td>
<td>.32</td>
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</tbody>
</table>

Abbreviations: CA, concomitant antibiotics; CDI, Clostridium difficile infection; REA, restriction endonuclease analysis.

a P-value comparing patients with BI isolates and patients with non-BI isolates.

b P-value comparing patients with isolates (BI and non-BI) and patients with no isolates.
c Previous CDI episode within 3 months prior to enrollment in study.
d For recurrence, antibiotic exposure at any time was considered.

e Comorbidity includes patients with chronic obstructive pulmonary disease, heart failure or myocardial infarction, methicillin-resistant Staphylococcus aureus, renal insufficiency, or cancer; patients on dialysis; patients with hepatic failure; and patients who use proton pump inhibitors or H2 receptor antagonists.

Table 5. Multivariate Analysis of Factors Likely to Influence Clinical Cure or Recurrence (Per-Protocol Population, N = 999)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test Reference</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>REA group</td>
<td>BI group</td>
<td>0.48</td>
<td>.27–.85</td>
<td>.03</td>
<td>1.57</td>
<td>1.01–2.45</td>
<td>.046</td>
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<td></td>
<td>No isolate</td>
<td>0.68</td>
<td>.39–1.19</td>
<td>.95</td>
<td>0.91</td>
<td>.57–1.47</td>
<td>.70</td>
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<td>Age</td>
<td>&lt;65</td>
<td>0.88</td>
<td>.55–1.41</td>
<td>.58</td>
<td>1.36</td>
<td>.93–1.98</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td>≥65</td>
<td></td>
<td></td>
<td></td>
<td>1.82</td>
<td>1.15–2.87</td>
<td>.01</td>
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<tr>
<td>CDI history</td>
<td>One prior episodeb</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.29</td>
<td>1.29–4.07</td>
<td>.01</td>
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<td></td>
<td>No prior episode</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.37</td>
<td>.91–2.07</td>
<td>.13</td>
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<td>Region</td>
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<td>1.12</td>
<td>.60–2.09</td>
<td>.34</td>
<td>0.78</td>
<td>.43–1.39</td>
<td>.14</td>
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<td></td>
<td>United States</td>
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<tr>
<td>Antibiotic history prior to CDI treatment</td>
<td>Yes</td>
<td>0.79</td>
<td>.42–1.49</td>
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<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CA during treatment perioda</td>
<td>Yes</td>
<td>0.63</td>
<td>.38–1.03</td>
<td>.06</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>CA during treatment or follow-up perioda</td>
<td>Yes</td>
<td>1.57</td>
<td>1.03–2.39</td>
<td>.04</td>
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<tr>
<td>Comorbidityd</td>
<td>Yes</td>
<td>0.39</td>
<td>.19–.80</td>
<td>.01</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td></td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment</td>
<td>Fidaxomicin</td>
<td>1.21</td>
<td>.78–1.90</td>
<td>.40</td>
<td>0.45</td>
<td>.31–.65</td>
<td>&lt;.0001</td>
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<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
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</table>

Abbreviation: CA, concomitant antibiotics; CDI, Clostridium difficile infection; CI, confidence interval; NA, not applicable; OR, odds ratio; REA, restriction endonuclease analysis.

a For clinical cure, antibiotic exposure during the 10-day treatment period was considered, and for recurrence, antibiotic exposure at any time was considered.
b Previous CDI episode within 3 months prior to enrollment in study.
c Not applicable as predictor in multivariate analysis because it was not statistically significant in univariate analysis.
d Comorbidity includes patients with chronic obstructive pulmonary disease, heart failure or myocardial infarction, methicillin-resistant Staphylococcus aureus, renal insufficiency, or cancer; patients on dialysis; patients with hepatic failure; and patients who use proton pump inhibitors or H2 receptor antagonists.
evidence that the BI epidemic strain of C. difficile is more difficult to treat than other strains of C. difficile, which may explain in part the persistent perception of greater disease severity that was in prior large studies linked to the advanced age of the patients [15, 17]. Limitations of this study include the relatively low percentage of isolates recovered from patients for typing. Patients who did not have isolates had more comorbidities and were more likely to reside in the United States than those with isolates. The study also lacked data on intensive care unit care of patients and had a relatively short follow-up period for recurrence of 28 days. Unexplained is the higher cure rate for Canadian patients compared with US and European patients.

In summary, these data from 2 large phase 3 clinical trials of fidaxomicin vs vancomycin indicate that clinical cure rates for patients infected with the epidemic BI strain of C. difficile are significantly reduced in comparison with CDI caused by other C. difficile strains, and this reduced clinical cure occurred independent of the treatment agent used. Increased recurrence rates of CDI were also related to multivariate analysis to infection with the BI strain, with prior history of CDI, and with concomitant use of other antimicrobials. Laboratories can now rapidly identify patients with the BI/NAP1 strain of C. difficile using a specific PCR test [19]; however, it is not clear what the preferred treatment of such patients should be. More effective treatments of the epidemic BI/NAP1 strain are needed.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/our-journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Supplementary materials are available at http://cid.oxfordjournals.org/our-journals/cid/.

Notes

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Potential conflicts of interest. S. J. has served as a consultant for the following companies: ViroPharma, Optimer, Astellas, Pfizer, Cubist, and BioX+ D. N. G. holds patents for the treatment and prevention of CDI licensed to ViroPharma; is a consultant for ViroPharma, Optimer, Cubist, Merck, Pfizer, TheraDoc, Astellas, BioRelix, Canegene, Medicines Co. and Actelion; and holds research grants from GOJO, Merck, Optimer, Sanofi Pasteur, Eurofins Medinett, Actelion and ViroPharma. P. S. S., F. B., and Y. K. are employees of Optimer Pharmaceuticals, Inc. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References