SUPPLEMENT ARTICLE

Treatment of First Recurrence of *Clostridium difficile* Infection: Fidaxomicin Versus Vancomycin

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Recurrence of *Clostridium difficile* infection (CDI) occurs in approximately 25% of successfully treated patients. Two phase 3 randomized, double-blind trials were conducted at 154 sites in the United States, Canada, and Europe to compare fidaxomicin vs vancomycin in treating CDI. Patients with CDI received fidaxomicin 200 mg twice daily or vancomycin 125 mg 4 times daily for 10 days. The primary end point was clinical cure of CDI at end of treatment, and a secondary end point was recurrence during the 28 days following clinical cure. In all, 1164 subjects were enrolled, of which a subgroup of 128 in the per-protocol population had another recent episode of CDI prior to the CDI diagnosis at study enrollment. In the analysis of this subgroup, initial response to therapy was similar for both drugs (>90% cure). However, recurrence within 28 days occurred in 35.5% of patients treated with vancomycin and 19.7% of patients treated with fidaxomicin (−15.8% difference; 95% confidence interval, −30.4% to −0.3%; $P = .045$). Early recurrence (within 14 days) was reported in 27% of patients treated with vancomycin and 8% of patients treated with fidaxomicin ($P = .003$). In patients with a first recurrence of CDI, fidaxomicin was similar to vancomycin in achieving a clinical response at end of therapy but superior in preventing a second recurrence within 28 days.

***Clinical Trials Registration*.** NCT00314951 and NCT00468728.

Treatment of *Clostridium difficile* infection (CDI) with either metronidazole or vancomycin is associated with recurrence in 20%–30% of patients. Recurrence of disease is frustrating because there is no approved treatment alternative that provides a lower probability of yet another recurrence. Following a second recurrence, subsequent episodes occur in as many as 40%–60% of patients [1]. Recurrent CDI may be a consequence of resident spores or infection from local environmental contamination. Relapse and reinfection are therefore difficult to distinguish. Both metronidazole and vancomycin suppress the growth of the normal microflora and thereby defeat natural colonization resistance [1–5]. The purported success of fecal transplantation in the treatment of relapsing CDI supports the importance of preservation of the normal flora in preventing reinfection [6–8].

Current guidelines are to treat a first episode of nonsevere uncomplicated CDI with oral metronidazole 500 mg 3 times daily for 10–14 days [9, 10]. Oral vancomycin 125 mg 4 times daily for 10–14 days has become the standard for treating severe CDI. Treatment of the first recurrence of CDI is usually

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conducted with the same regimen used to treat the initial episode, whereas tapered and/or pulsed doses of vancomycin are recommended for second and subsequent recurrences. Long-term treatment with metronidazole has been associated with cumulative neurotoxicity and is not recommended beyond the first recurrence.

Fidaxomicin is highly active against Gram-positive anaerobes [11–13] and spares *Bacteroides* species that normally comprise a major constituent of fecal flora [4, 8]. In contrast, vancomycin and metronidazole have broader antimicrobial activity; vancomycin has been shown to reduce fecal *Bacteroides* counts by 3–4 logs [4].

Fidaxomicin has been compared with vancomycin for the treatment of CDI in 2 phase 3 trials [14, 15]. This report presents a subset analysis comparing the efficacy of fidaxomicin with the efficacy of vancomycin in preventing a second recurrence in patients who were enrolled in the trials after a recent single episode of CDI.

METHODS

Study Population

Patients with toxin-positive CDI were recruited to 2 phase 3 double-blind, randomized, controlled trials (NCT00314951 and NCT00468728). A separate stratum was constructed of patients who had experienced a single prior CDI episode within 3 months of the current CDI episode. Patients were recruited in the United States, Canada, and Europe. Eligible patients were aged >15 years, had a diagnosis of CDI, and had received no more than 24 hours of pretreatment with vancomycin or metronidazole. Concomitant treatment with other potentially effective treatments for CDI was not allowed. Of 1164 patients enrolled in both trials, 178 (15%) were enrolled for treatment of a first recurrence. *Clostridium difficile* infection was defined as a change in bowel habits, with >3 unformed bowel movements (or >200 mL of unformed stool for patients with rectal collection devices) in the 24 hours before randomization and the presence of *C. difficile* toxin A or B in the stool within 48 hours of randomization. All patients gave written informed consent.

Study Design and Conduct

Subjects were randomized in a 1:1 ratio to receive oral fidaxomicin (200 mg twice daily) or vancomycin (125 mg 4 times daily) for 10 days. The main outcome of this analysis was recurrence (diarrhea and positive stool toxin test) within 28 days after completing treatment. Patients were evaluable for recurrence if they were followed up for 28 ± 2 days from the end of treatment and did not receive additional CDI therapy. Results are given for the modified intent-to-treat (mITT) and per-protocol groups.

Fecal samples collected before the first dose of study drug, at the end of treatment, and at recurrence of symptoms were assayed for toxins A and B, which were assessed by the standard tests used at the local site laboratory. Patients were asked to record self-administration of study drugs and CDI symptoms, including number and consistency of bowel movements.

Safety was assessed by interview, recording of adverse events, physical examination, clinical laboratory tests, electrocardiograms, and other evaluations.

Study Drugs, Randomization, and Blinding

Study drugs were overencapsulated using microcrystalline cellulose as filler so that all capsules were identical in appearance and taste. Capsules were supplied to patients in blister packs with instructions on how to take the study medication during the 10-day treatment period. Patients randomized to receive fidaxomicin took 2 capsules containing 200 mg of fidaxomicin and 2 placebo capsules, alternating. Patients in the vancomycin treatment group took 4 capsules containing 125 mg of vancomycin. An interactive voice response system or an interactive web response system was used to assign a computer-generated randomization number and medication kit number to each patient. The investigator, sponsor and site personnel, and patients were blinded to treatment assignment.

Statistical Analysis

Patients with either a first episode of CDI or a single prior episode of CDI were enrolled, and this is a subset analysis of the latter, with no predetermined sample size.

To compare the efficacy of fidaxomicin vs vancomycin in preventing a second recurrence within 28 ± 2 days of completion of treatment for the first recurrent episode, a χ^2 test of difference in proportions was performed and 2-sided 95% confidence intervals (CIs) were derived. Recurrence was compared across subgroups according to age, sex, and inpatient status.

A Kaplan–Meier analysis using the Gehan–Wilcoxon and log rank tests was used to determine equality across treatment and age strata. A Cox proportional hazard model was used to determine if treatment (fidaxomicin or vancomycin), receipt of concomitant antibiotics, and age were predictors of recurrence, and corresponding adjusted hazard ratios (HRs) and 95% CIs were calculated. The treatment-by-age interaction term was included in the full model. If the interaction term was not statistically significant at $\alpha = 0.05$, a reduced model without the interaction term was used in the final model.

RESULTS

Patients

The mITT study population consisted of 178 enrolled patients who were randomized and received at least 1 dose of

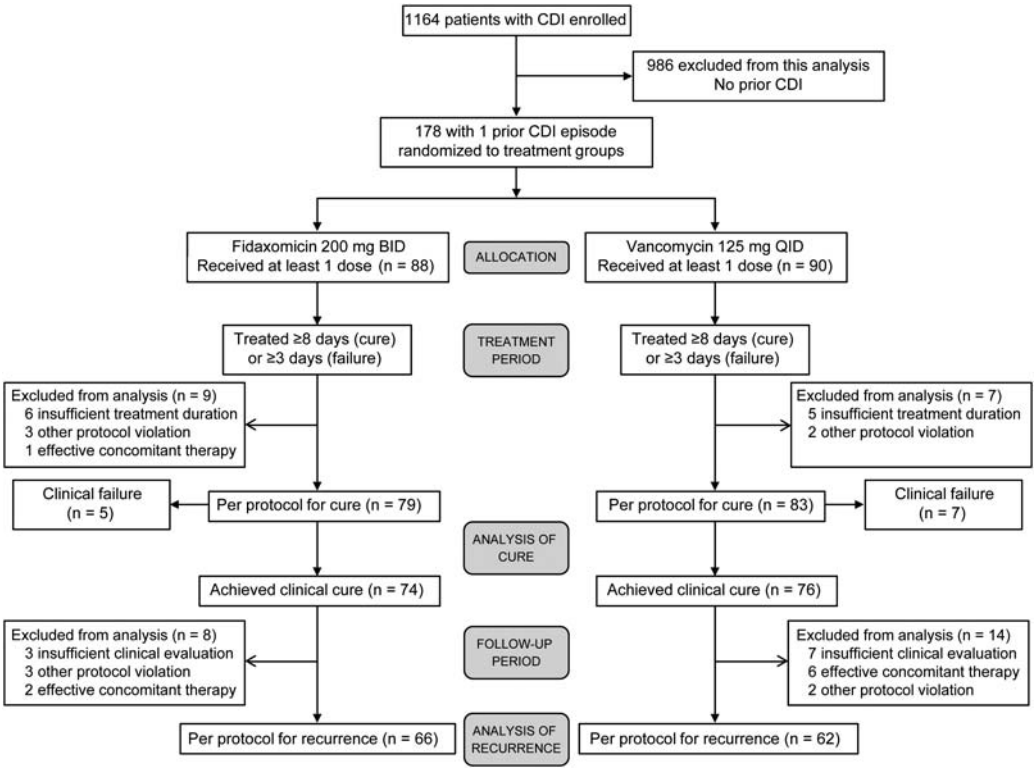

Figure 1. Disposition of patients. Patients could have >1 reason for exclusion from an analysis population. Abbreviations: BID, twice daily; CDI, *Clostridium difficile* infection; mITT, modified intent to treat; QID, 4 times daily.

fidaxomicin (88 patients) or vancomycin (90 patients) (Figure 1). There were 79 and 83 patients, respectively, in the per-protocol analysis of cure. Patients who were cured (74 fidaxomicin-treated and 76 vancomycin-treated patients) were monitored for recurrence. Eight patients in the fidaxomicin treatment arm and 14 patients in the vancomycin treatment arm were excluded from the per-protocol analysis of recurrence owing to insufficient follow-up, receipt of other therapy for CDI, or other protocol violations. There were 128 patients in the per-protocol analysis of recurrence, 66 treated with fidaxomicin and 62 treated with vancomycin. Table 1 summarizes baseline characteristics of the per-protocol population. Despite variability between groups because of the relatively small sample size, the difference was not significant for any treatment group comparison of baseline characteristics ($P > .05$).

Recurrence of CDI

The initial outcome of clinical cure was similar for the fidaxomicin and vancomycin treatment groups; response was 93.7% (74 of 79) for fidaxomicin and 91.6% (76 of 83) for vancomycin in per-protocol patients with a prior episode of CDI (Figure 1). The median number of days receiving the study drug was 10 for the 128 per-protocol patients evaluated for recurrence and the same for fidaxomicin (n = 66) and vancomycin (n = 62) treatment groups. Table 2 summarizes the incidence of recurrence according to prior CDI experience and treatment group. Patients with a prior episode of CDI were more likely to have a second recurrence within a month of completing either therapy. Incidence rates in patients with a prior episode were 19.7% (13 of 66) after fidaxomicin treatment and 35.5% (22 of 62) after vancomycin treatment. The absolute difference of 15.8% was significant ($P = .045$), and the relative difference was a 44% reduction in subsequent recurrence with fidaxomicin vs vancomycin treatment. These rates were 1.7-fold and 1.6-fold higher, respectively, than the frequencies of recurrence in patients with no prior episode; in the per-protocol population with no prior CDI experience, recurrence rates were 11.7% after fidaxomicin treatment and 22.6% after vancomycin treatment ($P < .001$).

Results were similar for the mITT population but were not statistically significant for the comparison of fidaxomicin with vancomycin ($P = .08$). A second recurrence occurred in 20.3% of fidaxomicin-treated patients and in 32.3% of vancomycin-treated patients, representing a 37% relative reduction with

Table 1. Baseline Characteristics of Patients With a First Recurrence of *Clostridium difficile* Infection

Characteristic	Fidaxomicin (n = 66)[a]	Vancomycin (n = 62)[a]	Total (N = 128)[a]
Age, years			
Mean ± SD	60.86 ± 18.17	64.63 ± 17.74	62.69 ± 17.99
Median (min, max)	60 (18, 90)	66 (22, 92)	63 (18, 92)
Age categories, No. (%)			
<65 years	36 (54.6)	30 (48.4)	66 (51.6)
≥65 years	30 (45.5)	32 (51.6)	62 (48.4)
Sex, No. (%)			
Male	32 (48.5)	25 (40.3)	57 (44.5)
Female	34 (51.5)	37 (59.7)	71 (55.5)
Patient status, No. (%)			
Inpatient	35 (53.0)	33 (53.2)	68 (53.1)
Outpatient	31 (47.0)	29 (46.8)	60 (46.9)
Strain, No. (% pts, % isolates)			
NAP1/BI/027	23 (34.9, 45.1)	16 (25.8, 35.6)	39 (30.5, 40.6)
Non-NAP1/BI/027	28 (42.4, 54.9)	29 (46.8, 64.4)	57 (44.5, 59.4)
Unknown (no isolate)	15 (22.7, NA)	17 (27.4, NA)	32 (25.0, NA)
ESCMID criteria[b]			
Nonsevere	54 (81.8)	46 (74.2)	100 (78.1)
Severe	12 (18.2)	16 (25.8)	28 (21.9)
Estimated creatinine clearance	n = 63	n = 60	N = 123
Mean ± SD (mL/min/1.73 m^2)	84.4 ± 38.3	79.9 ± 38.4	82.2 ± 38.2
<60 mL/min/1.73 m^2, No. (%)	17 (27.0)	18 (30.0)	35 (28.5)
Time since onset of prior CDI, days[a]	n = 55	n = 45	N = 100
Mean ± SD	34.8 ± 16.2	35.0 ± 17.6	34.9 ± 16.8
Median (min, max)	32 (9, 90)	31 (14, 96)	31.5 (9, 96)
Therapy for prior CDI, No. (%)			
None	10 (15.2)	12 (19.4)	22 (17.2)
Metronidazole	41 (62.1)	25 (40.3)	66 (51.6)
Vancomycin	10 (15.2)	13 (21.0)	23 (18.0)
Metronidazole + vancomycin	4 (6.1)	12 (19.4)	16 (12.5)
Metronidazole, vancomycin + rifaximin	1 (1.5)	0 (0)	1 (0.8)
Concomitant antibiotic use during study, No. (%)			
During treatment	9 (13.6)	7 (11.3)	16 (12.5)
During follow-up	9 (13.6)	6 (9.7)	15 (11.7)
At any time during study	12 (18.2)	9 (14.5)	21 (16.4)

Includes per-protocol patients with prior episode of *Clostridium difficile* infection who were cured by treatment and met criteria of evaluability for recurrence. $P > .05$ for fidaxomicin vs vancomycin for all baseline characteristics. Chi-square test was used for categorical variables and Student *t* test was used for continuous variables.

Abbreviations: CDI, *Clostridium difficile* infection; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; max, maximum; min, minimum; NA, not applicable; SD, standard deviation.

[a] Unless otherwise indicated; some baseline characteristics were not available for all patients.

[b] Severe: any 1 of the criteria of fever (body temperature >38.5°C), leukocytosis (white blood cell count $>15 \times 10^9$/L), or elevated serum creatinine level (>1.5 mg/dL); nonsevere, none of the criteria listed.

fidaxomicin. Recurrence rates were lower for patients with no prior episode—12.9% for fidaxomicin-treated patients and 24.8% for vancomycin-treated patients—and the difference between treatment groups was significant ($P < .001$).

Figure 2 represents a Kaplan–Meier analysis of time to recurrence of CDI following completion of treatment with fidaxomicin or vancomycin in per-protocol patients with a prior episode. As a group, patients whose CDI recurred following completion of fidaxomicin therapy had a longer time to recurrence than those completing vancomycin treatment (Table 3; $P = .01$). An analysis of recurrences at the midpoint of the 28-day follow-up period was done (Table 3). Following completion of vancomycin therapy, 17 patients (27%) had a recurrence within 14 days. After fidaxomicin treatment, only 5

Table 2. *Clostridium difficile* Infection Recurrence Following Successful Fidaxomicin or Vancomycin Treatment

	Proportion of Patients (n/N)		Absolute Difference (%)		
Population Subgroup	FDX	VAN	FDX-VAN	95% CI	*P* Value
Per protocol					
No prior episode, n = 666	11.7% (38/325)	22.6% (77/341)	−10.9	−16.5 to −5.2	<.001
1 prior episode, n = 128	19.7% (13/66)	35.5% (22/62)	−15.8	−30.4 to −0.3	.045
mITT					
No prior episode, n = 803	12.9% (51/395)	24.8% (101/408)	−11.8	−17.1 to −6.5	<.001
1 prior episode, n = 159	20.3% (16/79)	32.3% (26/80)	−12.3	−25.4 to 1.5	.08

Abbreviations: CI, confidence interval; FDX, fidaxomicin; mITT, modified intent to treat; VAN, vancomycin.

patients (8%) had a recurrence in the same time period ($P = .003$). These represent 77% (17 of 22) and 38% (5 of 13), respectively, of all recurrences in the 28-day period following completion of vancomycin or fidaxomicin therapy. From days 15 to 28, recurrence rates among the remaining symptom-free patients at day 14 were similar for the fidaxomicin (13%) and vancomycin (11%) treatment groups.

Factors Associated With Recurrence

Treatment with fidaxomicin was associated with a lower risk of recurrence and longer time to recurrence compared with vancomycin. Among the baseline characteristics, only age was associated with risk of recurrence. Age group and treatment group were independent predictors of recurrence ($P = .84$ for interaction). Figure 3 shows the per-protocol analysis of recurrence over time by age group in patients with prior CDI experience. Kaplan–Meier analysis indicated that patients aged ≥65 years were more likely to have a recurrence during weeks 2, 3, and 4 of follow-up than were younger patients, and the difference between the 2 groups was highly significant by log rank and Wilcoxon tests ($P = .006$ and $P = .01$, respectively). Patients aged ≥65 years were more than twice as likely to have a second recurrence during the 28-day follow-up period than patients aged <65 years (HR, 2.57; 95% CI, 1.26–5.25; $P = .01$), after adjusting for treatment arm and receipt of concomitant antibiotics (Table 4). Treatment with vancomycin significantly doubled the risk of a second recurrence compared with treatment with fidaxomicin (adjusted HR, 2.17; 95% CI, 1.09–4.34; $P = .03$), but receipt of concomitant antibiotics did not significantly influence recurrence in this population.

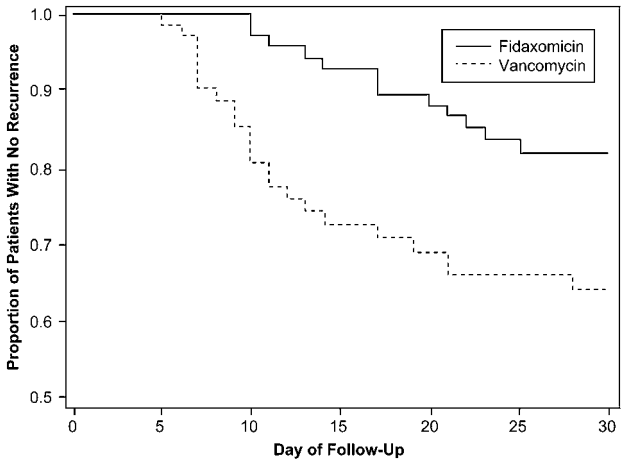

Figure 2. Time to recurrence by treatment group in patients with a prior episode of *Clostridium difficile* infection. Kaplan–Meier analysis of the probability of recurrence according to treatment group (per-protocol population). Day 0 is defined as the day the patient received the last dose of either fidaxomicin or vancomycin. The difference between treatment groups was statistically significant by both log rank ($P = .02$) and Wilcoxon ($P = .01$) tests.

Safety

Measures of safety were similar in the fidaxomicin and vancomycin treatment groups. Gastrointestinal and infectious conditions were the most commonly reported adverse events. Plasma levels of fidaxomicin and its main metabolite ranged from 20–50 ng/mL, and there was no accumulation at day 10 [16].

Table 3. Time to Recurrence Following Fidaxomicin vs Vancomycin Treatment in Patients With 1 Prior Episode of *Clostridium difficile* Infection

Endpoint	Fidaxomicin	Vancomycin	*P* Value
Cured and evaluated for recurrence	n = 66	n = 62	
Recurrence within 14 days of follow-up	5/66 (7.6%)	17/62 (27.4%)	.003
No recurrence within 14 days	n = 61	n = 45	
Recurrence from 15 to 28 days	8/61 (13.1%)	5/45 (11.1%)	
Censored at 28 days (no recurrence)	53/66 (80.3%)	40/62 (64.5%)	

Results are for the per-protocol population.

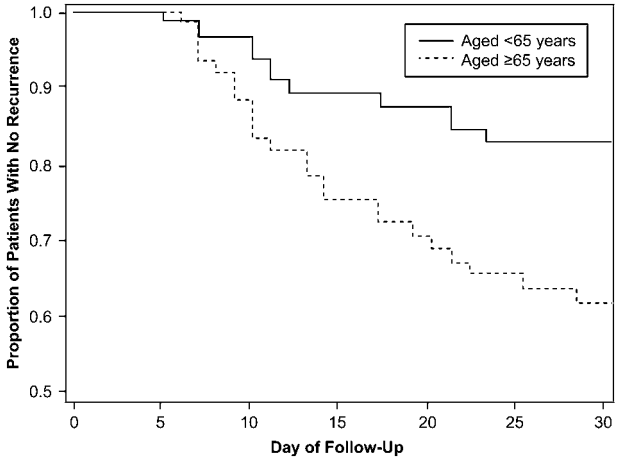

Figure 3. Time to recurrence by age group in patients with a prior episode of *Clostridium difficile* infection. Kaplan–Meier analysis of the probability of recurrence according to age group (per-protocol population). Day 0 is defined as the day the patient received the last dose of either fidaxomicin or vancomycin. The difference between age groups was statistically significant by both log rank ($P = .006$) and Wilcoxon ($P = .01$) tests.

DISCUSSION

Treatment of acute CDI with metronidazole or vancomycin is effective in many patients, but recurrent CDI in a subset of patients continues to present a significant clinical challenge [14]. The major contributing processes in recurrent CDI are postulated to be persistence of *C. difficile* spores that can germinate following completion of therapy, suppression or eradication of protective microflora that would normally inhibit germination and vegetative growth of resident spores or establishment of newly acquired environmental spores, and failure of the host to establish an adequate immune response to *C. difficile* toxins A and B [1, 17, 18]. Germination of persistent spores and relapse generally occur within 7–10 days of completion of antibiotic therapy for CDI [6], whereas mean time to reinfection from environmental sources has been estimated at 42.5 days [19]. Patients with chronic relapsing CDI typically have 7–15 days between cycles of antibiotics to treat reemergent symptoms, suggesting that these episodes represent regrowth from persistent spores rather than new infections [6, 19, 20].

A retrospective analysis of 463 patients in Quebec, Canada, presenting with a first recurrence of *C. difficile* between 1991 and mid-2005 found that the risk for a second recurrence within 60 days of diagnosis was similar whether patients were treated with metronidazole, vancomycin, or both for either the initial or first recurrent episode [21]. One-third of patients treated with either antibiotic had a second recurrence, and risk increased with age and duration of hospitalization. The risk of recurrence was similar to that in the present study, although duration of follow-up varied. In the Canadian study, 33% of patients had recurrence of CDI within 60 days of beginning vancomycin treatment, with the majority of those recurrences occurring within 30 days. In our study, recurrence after vancomycin was 35.5% within 28 days of completing therapy; this corresponds to 36–40 days from the first dose of vancomycin, depending on duration of follow-up (26–30 days). In contrast, patients treated with fidaxomicin in this study had a 19.7% risk of a second recurrence.

Table 4. Effect of Age on Time to Recurrence

Variable	Comparison	Hazard Ratio (95% CI)	*P* Value
Age	≥65 vs <65 years	2.57 (1.26–5.25)	.01
Treatment	Vancomycin vs fidaxomicin	2.17 (1.09–4.34)	.03
Concomitant antibiotics[a]	Yes vs no	1.36 (.59–3.13)	.47

Abbreviation: CI, confidence interval.

[a] Patient received ≥1 dose of oral or parenteral antibiotic with antibacterial activity at any time during the study.

A vexing issue is whether recurrence of CDI is caused by relapse with the original strain or reinfection with a new strain from the environment. In this randomized, blinded trial, we found that treatment of an initial recurrence with fidaxomicin was associated with fewer second recurrences than treatment with vancomycin. In addition, mean time to second recurrence was significantly longer in the fidaxomicin treatment group. Only 38% (5 of 13) of recurrences occurred within 14 days of completing fidaxomicin therapy, whereas 77% (17 of 22) of recurrences in the vancomycin group occurred by day 14. Because both drugs may remain in the large bowel for several days, it is postulated that the early reduction in recurrence represents prevention of relapse from germination of the resident *C. difficile* spores, and within this time frame, fidaxomicin was clearly more effective than vancomycin. However, CDI recurrence after 14 days, when both antibiotics have been cleared from the gut, more likely represents new infection from environmental sources, and the rates of recurrence after 14 days were similar for both drugs (13% of fidaxomicin-treated patients and 11% of vancomycin-treated patients without recurrence by day 14 of follow-up).

Advanced age was also associated with a second recurrence; patients aged ≥65 years were more than twice as likely to have a relapse in 28 days than patients aged <65 years. Other studies have observed an increased risk of recurrence within 2 months for patients aged ≥65 years following treatment with metronidazole [18, 22]. The relapse rate was as high as 58% in this age group during the Canadian outbreak in 2003–

2004 [22]. These studies did not stratify patients according to whether this was a first or subsequent episode of CDI. In the Canadian study, most recurrences in patients who remained hospitalized during the entire 60 days following initial diagnosis occurred within the first 30 days. Comparisons between studies and meta-analyses of recurrence are complicated by differences in methodology and duration of follow-up.

Oral administration of vancomycin or fidaxomicin results in high fecal concentrations of either drug, well above minimum inhibitory concentrations for all clinical isolates of *C. difficile*. In a study by Louie et al [4], mean *Bacteroides* counts in feces were similar at the beginning and end of fidaxomicin treatment (day 10), but use of vancomycin resulted in counts that were 3.8 logs lower following 10 days of treatment [4]. In specimens collected 21–28 days after the end of treatment, mean fecal spore counts were >2 logs lower in fidaxomicin-treated patients than in vancomycin-treated patients. Fidaxomicin spares most of the major phylogenetic clusters, including clostridial clusters XIVa and IV and *Bifidobacterium*, in contrast to vancomycin treatment [23].

Several therapeutic approaches have been tried in recurrent CDI, but published outcomes have been restricted by limited numbers of patients treated or retrospective analysis, often without adequate comparators. Standard vancomycin treatment followed by tapered and/or pulsed doses is recommended for second or subsequent recurrences [10, 24], but these regimens are not based on evidence from controlled studies. Another consideration is that a pulsed regimen could potentiate acquisition and overgrowth of vancomycin-resistant enterococci [25, 26]. Concomitant probiotic therapy has been proposed to improve the efficacy of antibiotics, but the evidence is scant [27].

Rifaximin treatment following a full course of vancomycin was effective in preventing recurrence in 7 of 8 patients with multiple recurrences of CDI, but 1 strain isolated from a patient posttherapy was resistant to rifaximin [28]. Several clinical isolates of *C. difficile* have been found to be resistant to rifaximin [14, 29–31]. The incidence of rifampin resistance during a CDI epidemic at 1 US teaching hospital was 37% for all clinical isolates and 82% for NAP1/BI/027 isolates [29]. Eight patients in that study had been exposed to rifamycins before developing a first episode of CDI, and 7 of those harbored rifampin-resistant *C. difficile*. Mutations in 1 region of the RNA polymerase β subunit (rpoB) gene of *C. difficile* confer resistance to both rifampin and rifaximin [31].

Fecal transplantation is reported to be effective in treating recurrent CDI, but the number of patients treated in published studies is small and no comparative trial has been reported [6–8]. Passive and active immunization approaches to treatment are also under investigation. In short, empirical approaches to treating recurrent CDI have been reported in a number of small case series and have been compared in retrospective analyses, but it is clear that prospective, randomized, controlled trials are needed to establish guidelines for the treatment of recurrent CDI [10].

Our results suggest that fidaxomicin or vancomycin treatment of a first recurrence of CDI produces similar initial relief of symptoms (>90% response), but fidaxomicin is superior in preventing a second recurrence within 28 days of completion of therapy. Preservation of the normal intestinal flora during fidaxomicin treatment is presumed to be a major factor in the difference in risk of recurrence. In trials to date, fidaxomicin has been safe and well tolerated, is minimally absorbed, is not associated with selection of antibiotic-resistant strains in vivo or in vitro, and is superior in reducing recurrences following vancomycin therapy. This subset analysis has shown that this relative superiority for preventing recurrences is also seen in patients with a recent single prior episode of CDI.

Notes

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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.

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