SUPPLEMENT ARTICLE

Reduced Acquisition and Overgrowth of Vancomycin-Resistant Enterococci and *Candida* Species in Patients Treated With Fidaxomicin Versus Vancomycin for *Clostridium difficile* Infection

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Fidaxomicin causes less disruption of anaerobic microbiota during treatment of *Clostridium difficile* infection (CDI) than vancomycin and has activity against many vancomycin-resistant enterococci (VRE). In conjunction with a multicenter randomized trial of fidaxomicin versus vancomycin for CDI treatment, we tested the hypothesis that fidaxomicin promotes VRE and *Candida* species colonization less than vancomycin. Stool was cultured for VRE and *Candida* species before and after therapy. For patients with negative pretreatment cultures, the incidence of VRE and *Candida* species acquisition was compared. For those with preexisting VRE, the change in concentration during treatment was compared. The susceptibility of VRE isolates to fidaxomicin was assessed. Of 301 patients, 247 (82%) had negative VRE cultures and 252 (84%) had negative *Candida* species cultures before treatment. In comparison with vancomycin-treated patients, fidaxomicin-treated patients had reduced acquisition of VRE (7% vs 31%, respectively; $P < .001$) and *Candida* species (19% vs 29%, respectively; $P = .03$). For patients with preexisting VRE, the mean concentration decreased significantly in the fidaxomicin group (5.9 vs 3.8 $\log_{10}$ VRE/g stool; $P = .01$) but not the vancomycin group (5.3 vs 4.2 $\log_{10}$ VRE/g stool; $P = .20$). Most VRE isolates recovered after fidaxomicin treatment had elevated fidaxomicin minimum inhibitory concentrations (MICs; MIC_{90}, 256 μg/mL), and subpopulations of VRE with elevated fidaxomicin MICs were common before therapy. Fidaxomicin was less likely than vancomycin to promote acquisition of VRE and *Candida* species during CDI treatment. However, selection of preexisting subpopulations of VRE with elevated fidaxomicin MICs was common during fidaxomicin therapy.

Clinical Trials Registration. NCT00314951.

Oral metronidazole and oral vancomycin are the agents most often prescribed for treatment of *Clostridium difficile* infection (CDI) [1]. Current practice guidelines recommend metronidazole for treatment of mild to moderate CDI and vancomycin for severe cases and in the setting of multiple recurrences [1, 2]. Although these antibiotics are effective in suppressing *C. difficile*, they are nonselective agents that also cause significant disruption of the indigenous microbiota of the colon [3–5]. For example, oral vancomycin achieves high concentrations in the intestinal tract, resulting in marked suppression of anaerobic organisms, including *Bacteroides* species [5, 6]. Such disruption of the indigenous microbiota may predispose

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patients to recurrent CDI and intestinal colonization by healthcare-associated pathogens such as vancomycin-resistant enterococci (VRE) and *Candida* species [7, 8]. In a previous study, we demonstrated that both oral metronidazole and oral vancomycin promoted persistent overgrowth of VRE in stool of patients with CDI with preexisting VRE colonization, resulting in frequent contamination of skin and environmental surfaces [3, 4]. Antibiotic-induced overgrowth of *Candida* species in the gastrointestinal tract is an important factor that predisposes to *Candida* infection and dissemination [8, 9]. These findings highlight the need for new CDI treatments that cause less disruption of the indigenous microbiota.

Fidaxomicin (formerly OPT-80) is a naturally occurring 18-member macrocycle being developed as a therapy for CDI [6, 10, 11]. Fidaxomicin is minimally absorbed after oral administration and achieves high concentrations in the intestinal tract [10, 11]. The compound has excellent in vitro activity against *C. difficile* (minimum inhibitory concentration required to inhibit the growth of 90% of organisms [MIC_{90}], 0.125 μg/mL), moderate activity against VRE (MIC_{90}, 4 μg/mL), but minimal activity against *Bacteroides* species (MIC_{90}, >1024 μg/mL) and other gram-negative organisms [6, 10, 11]. In a phase II clinical trial, fidaxomicin was effective in suppressing *C. difficile* but did not reduce *Bacteroides fragilis* group concentrations; in a separate group of patients with CDI, oral vancomycin treatment caused marked suppression of *Bacteroides* organisms [6]. In a phase III clinical trial, oral fidaxomicin was as effective as oral vancomycin for the treatment of CDI but was associated with a significantly reduced recurrence rate (13% vs 24%), presumably because it caused less disruption of the anaerobic microbiota [12]. Here, we tested the hypothesis that oral fidaxomicin promotes acquisition and overgrowth of VRE less than oral vancomycin because it has activity against many VRE species but lacks activity against many intestinal anaerobes, including *Bacteroides* species. To further investigate the importance of limiting alteration of the anaerobic microbiota during CDI therapy, we examined the effects of the treatment regimens on colonization by *Candida* species, because neither agent has activity against fungi and because the gastrointestinal tract is an important reservoir for *Candida* species.

METHODS

Setting and Study Design

The double-blind, randomized, phase III clinical trial of 10 days of fidaxomicin versus 10 days of vancomycin for treatment of CDI enrolled 548 subjects (265 were treated with fidaxomicin, and 283 were treated with vancomycin) in multiple hospitals in the United States and Canada [11] (Figure 1). Patients were given a diagnosis of CDI on the basis

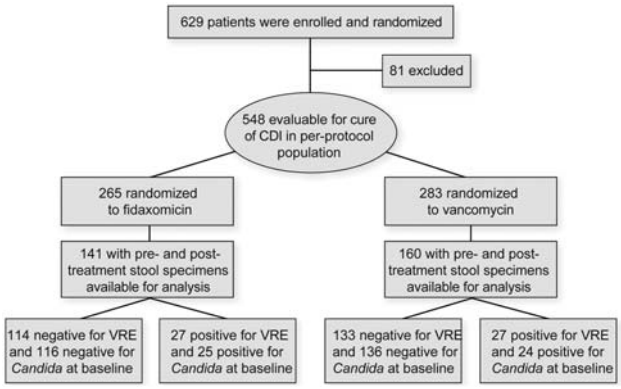

Figure 1. Flow diagram of subjects enrolled in the randomized trial of fidaxomicin versus vancomycin for treatment of *Clostridium difficile* infection and of the subset evaluated for acquisition and overgrowth of vancomycin-resistant enterococci and *Candida* species. Abbreviations: CDI, *Clostridium difficile* infection; VRE, vancomycin-resistant enterococci.

of symptoms of diarrhea and a positive result of a stool toxin assay, using commercial enzyme immunoassays. Patients with fulminant CDI or toxic megacolon were excluded. A randomly selected subset of patients had stool samples collected prior to and at the end of therapy for measurement of drug levels. The stool samples were frozen at −80°C. At the completion of the trial, the samples were transferred to a central laboratory for assessment of VRE and yeast colonization. Information regarding demographic characteristics, coexisting illnesses, and antibiotic therapy was collected prospectively through the standardized clinical study report. The Cleveland Veterans Affairs Medical Center's Institutional Review Board approved this laboratory study protocol.

Microbiology

Stool samples were serially diluted and plated on Enterococcosel agar (Becton Dickinson, Sparks, MD) containing 6 μg/mL of vancomycin and on Sabouraud dextrose agar (Becton Dickinson) to determine the presence and concentration of VRE and *Candida* species, respectively [7]. The limit of detection was approximately 1 $\log_{10}$ colony-forming unit (CFU) per gram of stool. Identification and susceptibility testing of VRE isolates was performed in accordance with Clinical Laboratory Standards Institute guidelines [13]. Yeast species that were acquired during CDI treatment were identified using VITEK 2 YST cards (bioMerieux, Marcy l'Etoile, France). *Enterococcus gallinarum* and *Enterococcus casseliflavus*, species that are intrinsically resistant to low concentrations of vancomycin, were excluded. For VRE isolates recovered at the highest level of dilution, broth-dilution MICs for vancomycin and fidaxomicin were determined using standard methods [12]. Because fidaxomicin resistance break points have not been established, we examined the change in fidaxomicin MICs for isolates recovered

before versus after fidaxomicin therapy. Broth-dilution MICs for rifampin were performed for all strains that were resistant to fidaxomicin 32 μg/mL. In addition, we tested the fidaxomicin susceptibility of a rifampin-resistant VRE strain that was selected through serial growth in the presence of subinhibitory concentrations of rifampin. For a subset of patients, levels of *Bacteroides* species were measured by plating dilutions onto Bacteroides Bile Esculin agar (Becton Dickinson).

Evaluation for Subpopulations of VRE With Elevated Fidaxomicin MICs Prior to Therapy

New detection of VRE with elevated fidaxomicin MICs after fidaxomicin therapy could represent de novo emergence of resistance (eg, mutations in RNA polymerase genes) or expansion of subpopulations of VRE with elevated MICs due to selective pressure during therapy. Therefore, we examined all stool samples obtained before therapy by using a replica plating method to determine whether subpopulations of VRE with elevated fidaxomicin MICs were present. Dilutions of stool samples were incubated for 48 hours on Enterococcosel agar containing vancomycin 20 μg/mL and then were transferred using sterile velvet onto Enterococcosel agar containing vancomycin 20 μg/mL plus fidaxomicin 32 μg/mL. The proportion of total VRE colonies that were resistant to fidaxomicin 32 μg/mL was calculated.

Statistical Analysis

Data were analyzed with the use of SPSS statistical software, version 10.0 (SPSS, Chicago, IL) and STATA 9.1 (StataCorp, College Station, TX). Distributions of clinical and demographic characteristics of patients treated with oral vancomycin versus oral fidaxomicin were compared. Unpaired *t* and Kruskal-Wallis tests were used for normally and nonnormally distributed data, respectively. The Pearson χ^2 and Fisher exact tests were used for categorical data. We compared proportions of patients who acquired VRE and *Candida* species colonization in each group. For patients with preexisting VRE colonization before treatment, we compared the proportions of patients who developed undetectable VRE levels at the end of therapy and the VRE concentrations before and after therapy. The concentrations of *Bacteroides* organisms in stool before and after therapy were compared for each treatment group. Proportions were compared using Pearson χ^2 and Fisher exact tests, and concentrations of organisms were compared using the Student paired *t* test.

RESULTS

Of 548 total patients enrolled in the trial, 301 (55%) had stool samples available both prior to and at completion of CDI therapy. Table 1 provides a comparison of the characteristics of the 160 vancomycin-treated patients and the 141 fidaxomicin-treated patients. There were no significant differences in age, clinical characteristics, and proportions of cases with severe disease or infected with epidemic BI *C. difficile* strains. With the exception of 1 *Enterococcus faecalis* isolate, all VRE isolates were *Enterococcus faecium*. The MICs of vancomycin for all VRE isolates tested were >256 μg/mL.

Acquisition of VRE and *Candida* Species Colonization During Treatment

Of 301 patients with CDI, 247 (82%) had negative cultures for VRE and 252 (84%) had negative cultures for *Candida* species prior to CDI treatment (Figure 1). In comparison with vancomycin-treated patients, fidaxomicin-treated patients had less frequent acquisition of VRE (8 of 114 patients [7%] vs 41 of 133

Table 1. Characteristics of 301 Patients With *Clostridium difficile* Infection Randomized to Receive Oral Fidaxomicin or Oral Vancomycin Therapy

Characteristic	Overall (n = 301)	Fidaxomicin (n = 141)	Vancomycin (n = 160)	*P*
Age, years, mean ± SD	60.9 ± 17.3	59.3 ± 17.0	62.4 ± 17.4	.11
Women	169 (56.2)	80 (56.7)	89 (55.6)	.85
Country: US (vs Canada)	188 (62.5)	84 (59.6)	104 (65.0)	.33
Initial infecting *C. difficile* strain restriction endonuclease type BI	78 (32.9)	35 (31.5)	43 (34.1)	.67
Severe CDI[a]	74 (24.6)	31 (22.0)	43 (26.9)	.33
Metronidazole treatment failure prior to enrollment	19 (6.3)	11 (7.8)	8 (5.0)	.32
Inpatient (vs outpatient)	160 (53.2)	73 (51.8)	87 (54.4)	.65
Received prior oral metronidazole or vancomycin therapy (<24 hours)	103 (34.2)	48 (34.0)	55 (34.4)	.95
Single prior episode of CDI (vs no prior episode)	52 (17.3)	23 (16.3)	29 (18.1)	.68
Unformed bowel movements per day at enrollment, no. mean (± SD)	8.4 ± 5.2	8.0 ± 4.1	8.7 ± 5.9	.24

Data are No. (%) of patients, unless otherwise indicated.

Abbreviations: CDI, *Clostridium difficile* infection; SD, standard deviation.

[a] Severe CDI was defined as a case with ≥1 of the following criteria: fever (temperature >38.5°C), leukocyte count >15 000 leukocytes/μL, and increase in serum creatinine level (>50% above the baseline level).

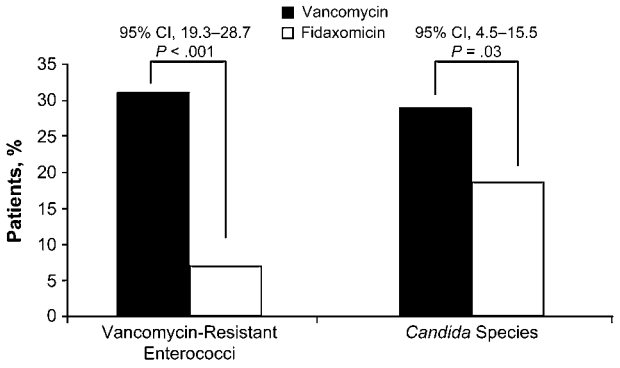

Figure 2. Percentages of patients with negative pretreatment cultures for vancomycin-resistant enterococci and *Candida* species who acquired VRE or *Candida* species in stool during treatment of *Clostridium difficile* infection with vancomycin or fidaxomicin. The lower limit of detection was approximately 1 $\log_{10}$ colony-forming units per gram of stool. *P* values and 95% confidence intervals are included for the differences between treatment groups in the primary end point. Abbreviation: CI, confidence interval.

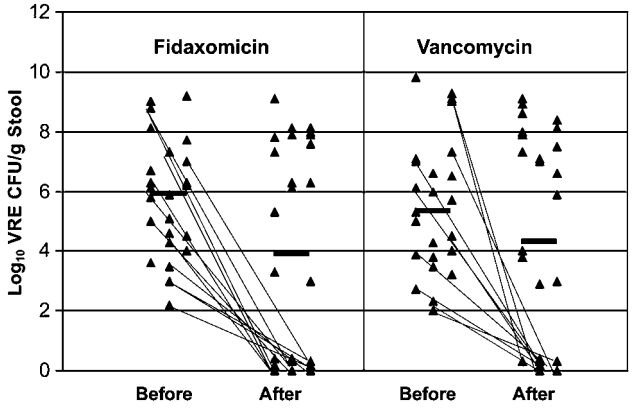

Figure 3. Change in concentration of vancomycin-resistant enterococci in stool of colonized patients during treatment of *Clostridium difficile* infection with vancomycin (n = 27) and fidaxomicin (n = 27). The thin lines connect pre- and posttreatment values for the subset of 12 fidaxomicin- and 10 vancomycin-treated patients with posttreatment concentrations less than the limit of detection (approximately 1 $\log_{10}$ colony-forming unit [CFU] per gram of stool). The thick horizontal lines show the mean concentration of VRE ($\log_{10}$ CFU/g of stool) for each group. Abbreviations: CFU, colony-forming unit; VRE, vancomycin-resistant enterococci.

patients [31%]; $P < .001$) and *Candida* species (22 of 116 patients [19%] vs 40 of 136 patients [29%]; $P = .03$) (Figure 2). For patients who acquired VRE, mean concentrations at the end of treatment were similar in the vancomycin and fidaxomicin treatment groups (mean [± standard deviation {SD}], 5.8 ± 0.5 and 5.8 ± 0.8 $\log_{10}$ CFU/g stool, respectively; $P = 1$). Four of the 8 fidaxomicin-treated patients (50%) were colonized with VRE isolates with fidaxomicin MICs ≥256 μg/mL, compared with only 4 of 41 vancomycin-treated patients (10%) ($P = .02$). Isolates with fidaxomicin MICs ≥32 μg/mL had variable susceptibility patterns to rifampin (MIC range, 0.06–64 μg/mL), suggesting that mutations leading to rifampin resistance were not responsible for the elevated fidaxomicin MICs. Moreover, a rifampin-resistant VRE strain (MIC, >256 μg/mL) selected through serial growth in the presence of subinhibitory concentrations of rifampin remained fully susceptible to fidaxomicin (MIC, 0.05 μg/mL).

For patients who acquired *Candida* species, mean concentrations at the end of treatment for the vancomycin and fidaxomicin groups were 4.5 and 4.4 $\log_{10}$ CFU/g stool, respectively ($P = .87$). Of 37 *Candida* species isolates subjected to speciation, 12 (32%) were *Candida albicans*, 20 (54%) were *Candida glabrata*, and 5 (14%) were other non-*albicans Candida* species.

Effect of CDI Treatment on Preexisting VRE Colonization

Fifty-four study patients (18%) had VRE stool colonization in the samples collected prior to the start of the study medications, of whom 27 were treated with vancomycin and 27 were treated with fidaxomicin. As shown in Figure 3, VRE concentrations were similar in both groups at baseline. The mean VRE concentration decreased significantly in the fidaxomicin group, from 5.9 to 3.8 $\log_{10}$ CFU/g stool (95% confidence interval [CI] for the difference in concentrations, 0.8–3.8 $\log_{10}$ CFU/g stool; $P = .01$). The mean VRE concentration decreased from 5.3 to 4.2 $\log_{10}$ CFU/g stool in the vancomycin group, but the difference was not statistically significant (95% CI for the difference in concentrations, −0.5 to 2.6 $\log_{10}$ CFU/g stool; $P = .20$). However, there was no difference in the proportion of patients for whom cultures performed by the end of treatment were negative for VRE (12 of 27 fidaxomicin-treated patients [44%] vs 10 of 27 vancomycin-treated patients [37%]; $P = .78$). For the fidaxomicin group, there was an increase in the fidaxomicin MICs of VRE isolates recovered before (MIC_{90}, 4 μg/mL; range, 2–256 μg/mL) versus after (MIC_{90}, 256 μg/mL; range, 1–>256 μg/mL) treatment. Replica plating experiments demonstrated that 9 of the 11 fidaxomicin-treated patients with new detection of isolates with fidaxomicin MICs >32 μg/mL had subpopulations (1%–10%) of VRE with similarly elevated MICs in samples prior to treatment. For vancomycin-treated patients for whom cultures performed by the end of treatment were negative for VRE, the vancomycin MICs of the initial VRE isolates ranged from 256 to 1024 μg/mL.

Effect of CDI Treatment on Preexisting *Candida* Species Colonization

Forty-nine study patients (16%) had *Candida* species stool colonization prior to the start of the study medications, of whom 25 were treated with vancomycin and 24 were treated with fidaxomicin. The mean concentration of *Candida* species

decreased significantly in the fidaxomicin (4.1 vs 2.1 $\log_{10}$ CFU/g stool; $P = .001$) and vancomycin (4.3 vs 3.2 $\log_{10}$ CFU/g stool; $P = .04$) groups. There was a nonsignificant trend toward more fidaxomicin-treated patients having negative culture results by the end of treatment (12 of 24 fidaxomicin-treated patients [50%] vs 6 of 25 vancomycin-treated patients [24%]; $P = 0.07$).

Effect of Treatment on Levels of *Bacteroides* Species in Stool

For 30 patients (15 per group), the effect of treatment on levels of *Bacteroides* species in stool was assessed. Prior to treatment, levels of *Bacteroides* organisms (mean [± SD], 4.8 ± 3.3 $\log_{10}$ CFU/g for the vancomycin group and 4.1 ± 1.2 $\log_{10}$ CFU/g for the fidaxomicin group) were low in comparison with typical levels for healthy humans [4]. Vancomycin treatment was associated with a further significant reduction in *Bacteroides* species levels (4.1–2.6 $\log_{10}$ CFU/g stool; $P < .001$), whereas levels increased during fidaxomicin treatment (4.8–6.1 $\log_{10}$ CFU/g stool; $P < .01$).

DISCUSSION

In a substudy conducted in conjunction with a randomized, double-blind clinical trial, we found that fidaxomicin was significantly less likely than vancomycin to promote acquisition of VRE (7% vs 31%) and *Candida* species (19% vs 29%) colonization during CDI treatment. This finding has important clinical and infection control implications. VRE is an important healthcare-associated pathogen in North America and Europe [6], and the intestinal tract is an important reservoir for *Candida* species infection, particularly in immunocompromised patients [8, 14]. Many patients with CDI who acquire VRE and *Candida* species colonization have multiple risk factors for the development of infection (eg, older age, immunocompromise, and presence of devices) [15]. In addition, patients with CDI pose a high risk for transmission of VRE because diarrhea is associated with increased shedding of VRE into the environment [4]. Oral vancomycin and metronidazole promote persistent high concentrations of VRE in stool, further increasing the risk for shedding of VRE into the environment and onto skin [4]. Our findings suggest that fidaxomicin may provide an effective alternative therapy for CDI that is less likely to promote colonization with VRE and *Candida* species.

It is microbiologically plausible that fidaxomicin may be less likely than vancomycin to promote colonization with VRE and other pathogens. We demonstrated that oral vancomycin treatment significantly reduced *Bacteroides* levels in stool, whereas fidaxomicin treatment did not. These data are consistent with the findings of Louie et al [6]. We also found that many VRE strains in North American hospitals are susceptible to low levels of fidaxomicin. The inhibitory activity against VRE may prevent the establishment of colonization by susceptible strains. Notably, of the 7 fidaxomicin-treated patients who acquired VRE, 4 (57%) acquired isolates with elevated fidaxomicin MICs. Because neither fidaxomicin nor vancomycin has inhibitory activity against fungi, the differences in inhibition of anaerobic intestinal bacteria by these agents are likely to explain the lower frequency of acquisition of *Candida* species in the fidaxomicin group. The reduction in concentrations of preexisting *Candida* species in patients treated with fidaxomicin may be due to recovery of *Bacteroides* species and other anaerobes; however, it should be noted that a statistically significant but more modest reduction in *Candida* species was also seen in the vancomycin group.

Nearly 20% of patients with CDI were colonized with VRE prior to initiation of CDI therapy. It is likely that this percentage would have been even higher if only US hospitals had been included in the study. In 2 previous studies in hospitals in California and Cleveland, Ohio, prevalences of coexisting VRE colonization at the time of CDI diagnosis were 41% and 62%, respectively [2, 16]. In 44% of patients with preexisting VRE colonization, fidaxomicin therapy was associated with a reduction in VRE concentration to undetectable levels. For fidaxomicin-treated patients with persistent VRE colonization at the end of treatment, the fidaxomicin MICs of VRE isolates were higher at the end of treatment (MIC_{90}, 256 μg/mL; range, 1–>256 μg/mL) than prior to treatment (MIC_{90}, 4 μg/mL; range, 2–256 μg/mL), suggesting that resistance to fidaxomicin had emerged during therapy. The presence of fidaxomicin resistance did not correlate with rifampin resistance, suggesting that mutations leading to rifampin resistance are not responsible for the elevated fidaxomicin MICs.

Our data suggest that the new detection of VRE with elevated fidaxomicin MICs after fidaxomicin therapy may be due to expansion of subpopulations of VRE with elevated fidaxomicin MICs due to selective pressure during therapy rather than to de novo emergence of resistance (eg, mutations in RNA polymerase genes). We found that a majority of patients colonized with VRE with elevated fidaxomicin MICs after therapy had detectable minor subpopulations of these organisms present in stool samples prior to therapy.

Surprisingly, we found that vancomycin treatment was associated with reduction of VRE to undetectable levels in 37% of patients. Because oral vancomycin treatment results in high concentrations in the intestinal tract that are higher than the MICs of many VRE strains, it is possible that vancomycin might have eliminated colonization or suppressed VRE levels below the limit of detection (approximately 1 $\log_{10}$ CFU/g of stool) in some patients. The reduction in VRE was not

attributable to relatively low MICs in the preexisting VRE strains (vancomycin MIC range, 25–1024 μg/mL). In contrast to the present study, we found that vancomycin therapy was associated with reductions in preexisting VRE to undetectable levels in only 1 of 19 colonized patients in a previous study in a Veterans Affairs hospital [3].

Our study has some limitations. Assessment of acquisition of VRE and *Candida* species was based on stool samples obtained at the end of treatment, so subsequent acquisition occurring after CDI treatment could have occurred in some patients. However, for many of the study patients, additional stool samples were analyzed after completion of therapy, and results were similar to those for samples obtained at the end of therapy (data not shown). Because all patients were treated for CDI, there was no untreated control group. Therefore, we cannot definitively state that the vancomycin or fidaxomicin therapy was the cause of VRE or *Candida* species acquisition or persistence (ie, other antibiotics received prior to the diagnosis may have contributed). However, we have previously demonstrated that the concentration of VRE in stool of colonized patients decreases significantly by 1–2 weeks after discontinuation of antibiotic treatment [7].

In summary, we found that fidaxomicin did not suppress *Bacteroides* organisms and was less likely than vancomycin to promote acquisition of VRE or *Candida* species during CDI treatment. However, the ability of fidaxomicin to suppress established VRE colonization appeared to be limited because of the selection of subpopulations of VRE with elevated MICs to fidaxomicin. Additional studies are needed to determine whether fidaxomicin is less likely than vancomycin to promote colonization with other healthcare-associated pathogens (eg, antimicrobial-resistant gram-negative bacilli) and to assess whether use of fidaxomicin for CDI therapy will be associated with reduced risk for VRE and *Candida* species infection and transmission. There is also a need for studies to determine the mechanism of fidaxomicin resistance in VRE strains.

Notes

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Potential conflicts of interest. C. J. D. is a consultant for ViroPharma, Optimer, Merck, and GOJO and has received research grants from ViroPharma, Ortho-McNeil, and Pfizer. M. A. M. is a consultant for Optimer Pharmaceuticals. F. B. is an employee of Optimer Pharmaceuticals. 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.

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