ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5194–5199 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00625-11

Comparative Susceptibilities to Fidaxomicin (OPT-80) of Isolates Collected at Baseline, Recurrence, and Failure from Patients in Two Phase III Trials of Fidaxomicin against *Clostridium difficile* Infection▽

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Received 4 May 2011/Returned for modification 20 July 2011/Accepted 3 August 2011

A 10-day course of oral fidaxomicin (200 mg twice a day [b.i.d.]), a potent new macrocyclic drug, was compared to vancomycin (125 mg four times a day [q.i.d.]) in 1,164 adults (1,105 in the modified intent-to-treat [mITT] population) with *Clostridium difficile* infection in two phase III randomized, double-blind trials at sites in North America and 7 European countries. Of 1,105 mITT patients, 792 (71.7%), including 719/999 (72.0%) in the per-protocol (PP) population, provided a *C. difficile* strain at baseline, of whom 356 received fidaxomicin with 330 cures (92.7%) and 363 received vancomycin with 329 cures (90.6%). The susceptibilities (MIC_{90}) of baseline isolates did not predict clinical cure, failure, or recurrence for fidaxomicin (MIC_{90}, 0.25 μg/ml for both; range, ≤0.007 to 1 μg/ml), but there was a one-dilution difference in the MIC_{90} (but not the MIC_{50}) for vancomycin (MIC_{90}, 2 μg/ml [range, 0.25 to 8 μg/ml] for cure and 4.0 μg/ml [range, 0.5 to 4 μg/ml] for failures). A total of 65 (7.9%) "rifaximin-resistant" (MIC > 256 μg/ml) strains were isolated in both treatment groups on enrollment, which increased to 25% for failures at the end of therapy. No resistance to either fidaxomicin or vancomycin developed during treatment in either of the phase III studies, although a single strain isolated from a cured patient had an elevated fidaxomicin MIC of 16 μg/ml at the time of recurrence. All isolates were susceptible to ≤4 μg/ml of metronidazole. When analyzed by restriction endonuclease analysis (REA) type, 247/719 (34.4%) isolates were BI group isolates, and the MICs were generally higher for all four drugs tested (MIC_{90}s: fidaxomicin, 0.5; vancomycin, 2.0; metronidazole, 2.0; and rifaximin, >256 μg/ml) than for the other REA types. There was no correlation between the MIC of a baseline clinical isolate and clinical outcome. MIC_{90}s were generally low for fidaxomicin and vancomycin, but BI isolates had higher MICs than other REA group isolates.

Clostridium difficile infection has become an increasingly common and serious threat to patients in the hospital and the community, with approximately 600,000 cases annually in the United States (3). The emergence of a new and more potent toxin-producing epidemic strain (known as BI/NAP1/027, depending on the typing method) resulted in increased mortality of hospitalized patients, many of whom were elderly (12). Its initial presentation often went unrecognized until the patient was toxic and had an elevated white blood cell (WBC) count and a marked ileus.

Current recommended treatment for *C. difficile* infection is metronidazole for mild to moderate infection, although response to therapy with metronidazole has been reported to be lower than that with vancomycin for more severe infection (2, 8, 23). Guidelines suggest the use of vancomycin only for severe primary infections and recurrences because of the potential for emergence of vancomycin-resistant enterococci and, more recently, of decreased *Staphylococcus aureus* susceptibility to vancomycin (MIC creep) (8, 19). There is also a cost differential between vancomycin and metronidazole that favors metronidazole. Response to these therapies is often slow, recurrences occur in approximately 20% of patients (19), and transient resistance and heteroresistance to metronidazole have been reported (12, 15, 20). Consequently, there is an unmet medical need for the development of more effective treatments that will improve response and reduce clinical recurrence.

Fidaxomicin (formerly OPT-80 or PAR-101) is a potent new macrocyclic antibiotic that targets RNA polymerase (21). The drug has a narrow spectrum of activity, with no activity against Gram-negative bacteria and many anaerobes but high activity against *C. difficile* (1, 4, 13, 22). Fidaxomicin achieves a high concentration in the gut and has minimal systemic absorption. Against 110 toxigenic strains, Hecht et al. (14) found fidaxomicin had an MIC_{90} of 0.125 μg/ml compared with 0.5 and 2 μg/ml for metronidazole and vancomycin, respectively.

We report the comparative fidaxomicin and other susceptibilities of isolates collected at baseline, failure, and recurrence from patients in two recent phase III trials of *C. difficile* infection.

MATERIALS AND METHODS

In two randomized, double-blind phase III trials (referred to as studies 003 and 004), fidaxomicin was compared with vancomycin in subjects with *C. difficile* infection from sites across North America (United States and Canada) only in study 003 and in North America and 7 European countries (Belgium, France, Germany, Italy, Spain, Sweden, and the United Kingdom) in study 004 (10, 18).

Men and women (aged ≥16 years) with >3 diarrheal (liquid or unformed)

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▽ Published ahead of print on 15 August 2011.

TABLE 1. Summary of susceptibilities of baseline isolates by treatment group and antibiotic primary clinical outcome of cure (PP population)

Treatment group[a]	No. of patients	Geometric mean (range)	MIC_{50} (μg/ml)	MIC_{90} of 027/BI/NAP1 (μg/ml)
FDX				
Cure	330	0.10 (0.007–1.0)	0.125	0.25
Failure	26	0.13 (0.015–0.5)	0.125	0.25
VAN				
Cure	329	0.94 (0.25–8.0)	1	2
Failure	34	1.18 (0.5–4.0)	1	4

[a] FDX, fidaxomicin; VAN, vancomycin.

TABLE 2. Summary of susceptibilities of baseline isolates by treatment group and antibiotic, secondary clinical outcome of recurrence (PP population)

Treatment group[a]	No. of patients	Geometric mean (range)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
FDX				
Nonrecurrence	256	0.09 (0.007–1.0)	0.125	0.25
Recurrence	40	0.14 (0.015–0.5)	0.125	0.25
VAN				
Nonrecurrence	213	0.94 (0.25–8.0)	1	2
Recurrence	80	0.89 (0.25–2.0)	1	2

[a] FDX, fidaxomicin; VAN, vancomycin.

stools/day, with a positive enzyme immunoassay for *C. difficile* toxin or cell cytotoxicity assay, and with no more than 24 h of prior treatment for *C. difficile* were eligible for enrollment. Only patients with a primary episode or first recurrence of disease were eligible. Metronidazole, but not vancomycin, failures were eligible for enrollment. Patients with ileus, a WBC count of $>30 \times 10^9$/liter, toxic megacolon, or concern about life-threatening *C. difficile* infection were excluded from study entry. Patients with severe underlying disease who were not expected to survive for 72 h, regardless of cause; who had had more than a single *C. difficile* infection occurrence within 3 months; or who had Crohn's disease or ulcerative colitis also were excluded (18).

Patients were randomized to receive either fidaxomicin (200 mg orally twice daily) or vancomycin (125 mg orally four times daily) for 10 days. They were evaluated for clinical cure at the end of therapy and for recurrence out to 4 weeks following the end of treatment.

Stool samples were collected at entry (baseline) and at treatment failure or recurrence. *C. difficile* strains were isolated from the stool on cycloserine-cefoxitin fructose with taurocholate and horse blood agar in an anaerobic chamber. Colonies with typical *C. difficile* morphology were subcultured on supplemented (hemin and vitamin K_1) brucella agar, and their identity was confirmed via colony morphology, Gram's stain, and a positive proline test result. Susceptibilities of isolates to fidaxomicin, vancomycin, metronidazole, and rifaximin were determined by Clinical and Laboratory Standards Institute agar dilution methods (6, 7). *C. difficile* typing was performed via restriction endonuclease analysis (REA) by the method of Clabots et al. (5).

RESULTS

A total of 1,164 patients were enrolled (629 in study 003 and 535 in study 004) with a total of 1,105 in the modified intent-to-treat (mITT) group (596 in study 003 and 509 in study 004) and 999 in the per-protocol (PP) group (548 in study 003 and 451 in study 004). Seven hundred ninety-two of 1,105 patients (71.7%) in the mITT group and 719 of 999 (72.0%) patients in the PP group had a strain of *C. difficile* isolated from their baseline stool cultures, which forms the basis of this report. In the mITT population, 396 patients received treatment with fidaxomicin and 350 (88.4%) were cured; 395 received treatment with vancomycin, and 344 (86.9%) were cured. Similar results were observed for the PP population (fidaxomicin, 330/356 [92.7% cured]; vancomycin, 329/363 [90.6% cured]).

The susceptibilities (MIC_{90}) of baseline isolates did not predict clinical cure or failure for fidaxomicin-treated patients (MIC_{90}, 0.25 μg/ml for both groups; range, ≤0.008 to 1 μg/ml), nor did the MIC_{90} predict recurrences versus nonrecurrences for fidaxomicin (both 0.25 μg/ml). There was a 1-dilution difference in the MIC_{90} between cures and failures for vancomycin-treated patients (2 μg/ml for cures versus 4 μg/ml for failures), but not for recurrences versus nonrecurrences (2 μg/ml). However, as the geometric means, ranges, and MIC_{50}s are similar, these differences were not meaningful (Tables 1 and 2).

No resistance to fidaxomicin or vancomycin developed during treatment in either study. In one instance, a single strain was isolated from a cured patient at the time of recurrence that had an elevated fidaxomicin MIC of 16 μg/ml. This patient was enrolled with a *C. difficile* strain having a fidaxomicin MIC of 0.06 μg/ml. The patient was cured but culture positive at the end of therapy, and the strain had the same fidaxomicin MIC at the end of therapy as at the start. The patient had a recurrence 6 days after the last dose of study drug, and the strain isolated at that time had an MIC of 16 μg/ml. The typing method did not discriminate between the strains identified at baseline and recurrence (all were nonspecific REA groups). The clinical significance of this microbiological finding is unknown, particularly as fecal concentrations of fidaxomicin following oral dosing are in excess of 1,000 μg/g of feces.

MIC_{90}s were generally low (0.25 μg/ml for fidaxomicin, 1 μg/ml for metronidazole, and 2 μg/ml for vancomycin), with some variability between REA groups. It was observed that BI group baseline isolates had MIC_{90}s that were 1 dilution higher than the average across all strains for fidaxomicin (0.5 μg/ml) and metronidazole (2 μg/ml), consistent with prior phase 2 studies (4). There was a marked difference noted for rifaximin, for which the MIC_{90} for all REA groups was 0.125 μg/ml but >256 μg/ml for BI strains, CF strains, and K strains (Table 3).

No notable geographic differences (Table 4) in susceptibilities were observed, except for rifaximin, for which the overall U.S. MIC_{90} was >256 μg/ml compared with 0.060 μg/ml for Canada. In Europe, "resistance" (MIC > 256 μg/ml) to rifaximin was found in German and Italian strains, but not in strains from Belgium, France, Spain, Sweden, or the United Kingdom. Rifaximin "resistance" (MIC > 256 μg/ml) was encountered in 7.9% of strains on pretreatment specimens and was 20% for end-of-therapy failure strains. Of note, the vancomycin MIC_{90} for 17 German strains was 4 μg/ml, and the highest vancomycin MIC observed in a BI strain was 4 μg/ml.

No differences were present between the $MIC_{50/90}$ for metronidazole of patients admitted as metronidazole failures and those who were not failures, and susceptibilities to vancomycin and fidaxomicin were also similar (Table 5). Resistance to rifaximin (MIC > 256 μg/ml) was present in both patients admitted as metronidazole failures and those who were not.

TABLE 3. Susceptibility profiles of REA groups isolated at baseline (PP population)

REA group[a]	No. of patients	Antibiotic[b]	Geometric mean (range)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
BI	247	FDX	0.18 (0.015–1)	0.25	0.5
		VAN	1.04 (0.5–8)	1	2
		MTZ	0.85 (0.125–4)	1	2
		RIF	0.05 (0.003–>256)	0.015	>256
BK	12	FDX	0.09 (0.03–0.25)	0.06	0.125
		VAN	1.19 (1–2)	1	2
		MTZ	0.45 (0.25–2)	0.5	1
		RIF	0.03 (0.003–>256)	0.015	0.015
CF	7	FDX	0.09 (0.015–0.25)	0.125	0.25
		VAN	0.82 (0.5–2)	1	2
		MTZ	0.36 (0.05–1)	0.5	1
		RIF	0.06 (0.008–>256)	0.015	>256
DH	4	FDX	0.25 (0.25–0.25)	0.25	0.25
		VAN	1.00 (1–1)	1	1
		MTZ	0.50 (0.25–1)	0.5	1
		RIF	0.01 (0.003–0.015)	0.003	0.015
G	54	FDX	0.08 (0.015–0.25)	0.06	0.125
		VAN	0.95 (0.5–2)	1	2
		MTZ	0.31 (0.05–1)	0.25	0.5
		RIF	0.01 (0.003–0.125)	0.008	0.015
J	43	FDX	0.02 (0.007–0.125)	0.02	0.125
		VAN	0.98 (0.5–4)	1	2
		MTZ	0.41 (0.05–2)	0.5	1
		RIF	0.03 (0.003–>256)	0.015	0.06
Nonsp REA	259	FDX	0.08 (0.003–0.5)	0.06	0.125
		VAN	0.94 (0.25–4)	1	2
		MTZ	0.33 (0.02–2)	0.25	1
		RIF	0.02 (0.003–>256)	0.008	0.125
K	15	FDX	0.07 (0.015–0.25)	0.06	0.125
		VAN	1.10 (0.5–4)	1	2
		MTZ	0.69 (0.125–4)	0.5	4
		RIF	0.11 (0.004–>256)	0.015	>256
Y	77	FDX	0.10 (0.015–0.5)	0.125	0.25
		VAN	0.83 (0.25–2)	1	2
		MTZ	0.38 (0.06–2)	0.5	1
		RIF	0.01 (0.003–0.125)	0.008	0.015
All strains	719	FDX	0.10 (0.003–1)	0.125	0.25
		VAN	0.97 (0.25–8)	1	2
		MTZ	0.48 (0.02–4)	0.5	1
		RIF	0.02 (0.003–>256)	0.015	0.125

[a] A single L group isolate had MICs (μg/ml) of 0.13 for FDX, 0.50 for VAN, 0.50 for MTZ, and 0.13 for RIF.
[b] FDX, fidaxomicin; MTZ, metronidazole; Nonsp, nonspecific; RIF, rifaximin; VAN, vancomycin.

DISCUSSION

Since the start of the new millennium, there has been a dramatic increase in the severity and recurrence rates of *C. difficile* infection in North America and Europe, in part related to the emergence of the epidemic strain (BI/NAP1/027) (12). Given the reduced effectiveness of metronidazole and the substantial recurrence rate with both metronidazole and vancomycin, there is a need for more efficacious drugs, especially in other classes. Louie et al. (18) reported that clinical cure with fidaxomicin was "noninferior" to that with vancomycin and that "significantly fewer" fidaxomicin-treated patients than vancomycin-treated patients ($P = 0.004$) had recurrences of *C. difficile* infection, most notably with non-BI strains.

Six studies have reported on the activity of fidaxomicin against *C. difficile* isolates (1991 to 2007) (1, 9, 13, 14, 17, 22). In 2004, Ackermann et al. (1) tested 207 clinical *C. difficile* strains from Germany using a broth microdilution method and found all were susceptible to ≤0.006 μg/ml of fidaxomicin; Finegold et al. (13) tested 23 strains and reported an MIC_{90} of 0.25 μg/ml for fidaxomicin, but at least one strain had an MIC of 2 μg/ml (not further described). In 2007, Hecht et al. (14) reported on the activity of fidaxomicin against 110 toxigenic *C.*

TABLE 4. Summary of susceptibilities of baseline isolates by treatment group, geographic region, and antibiotic (PP population)

Geographic region[a]	*n*	Antibiotic[b]	Geometric mean (range)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
CA					
Ontario	48	FDX	0.12 (0.07–0.5)	0.125	0.25
		VAN	1.04 (0.5–4)	1	2
		MTZ	0.68 (0.06–4)	1	2
		RIF	0.01 (0.003–0.03)	0.015	0.015
Quebec	160	FDX	0.12 (0.015–1)	0.125	0.25
		VAN	1.01 (0.5–4)	1	2
		MTZ	0.48 (0.06–4)	0.5	1
		RIF	0.01 (0.003–>256)	0.008	0.015
West	113	FDX	0.07 (0.007–0.5)	0.06	0.25
		VAN	0.75 (0.25–2)	1	1
		MTZ	0.31 (0.02–4)	0.25	0.5
		RIF	0.01 (0.003–0.125)	0.008	0.060
EU					
Belgium	21	FDX	0.14 (0.015–0.5)	0.125	0.25
		VAN	1.26 (0.5–2)	1	2
		MTZ	0.48 (0.25–1)	0.5	1
		RIF	0.01 (0.003–0.015)	0.008	0.015
France	13	FDX	0.12 (0.007–0.5)	0.125	0.25
		VAN	1.24 (0.5–2)	1	2
		MTZ	0.56 (0.25–1)	0.5	1
		RIF	0.01 (0.003–0.03)	0.008	0.015
Germany	17	FDX	0.04 (0.007–0.125)	0.06	0.125
		VAN	1.57 (1–4)	1	4
		MTZ	0.64 (0.125–2)	0.5	1
		RIF	0.03 (0.003–>256)	0.015	>256
Italy	21	FDX	0.06 (0.02–0.125)	0.06	0.125
		VAN	1.26 (0.5–2)	1	2
		MTZ	0.38 (0.25–2)	0.25	1
		RIF	8.30 (0.003–>256)	>256	>256
Spain	2	FDX	0.13 (0.125–0.125)	0.125	0.125
		VAN	1.00 (1–1)	1	1
		MTZ	0.35 (0.25–0.5)	0.25	0.5
		RIF	0.01 (0.008–0.015)	0.008	0.015
Sweden	8	FDX	0.10 (0.015–0.25)	0.125	0.25
		VAN	1.19 (0.5–2)	1	2
		MTZ	0.59 (0.25–1)	0.5	1
		RIF	0.01 (0.003–0.015)	0.015	0.015
United Kingdom	37	FDX	0.08 (0.007–0.5)	0.125	0.25
		VAN	1.00 (0.25–4)	1	2
		MTZ	0.45 (0.05–2)	0.5	1
		RIF	0.01 (0.003–0.015)	0.008	0.015
United States					
Midwest	131	FDX	0.11 (0.008–0.5)	0.125	0.25
		VAN	0.96 (0.25–4)	1	2
		MTZ	0.53 (0.05–4)	0.5	1
		RIF	0.05 (0.003–>256)	0.015	>256
Northeast	23	FDX	0.11 (0.03–0.25)	0.125	0.25
		VAN	1.03 (0.5–4)	1	2
		MTZ	0.83 (0.25–2)	1	2
		RIF	0.36 (0.008–>256)	0.03	>256
South	92	FDX	0.11 (0.015–0.5)	0.125	0.25
		VAN	0.85 (0.25–4)	1	2
		MTZ	0.5 (0.5–4)	0.5	1
		RIF	0.03 (0.003–>256)	0.015	0.125
West	39	FDX	0.1 (0.003–0.5)	0.125	0.5
		VAN	1.05 (0.25–8)	1	2
		MTZ	0.51 (0.125–2)	0.5	2
		RIF	0.08 (0.008–>256)	0.015	>256

[a] CA, Canada; EU, European Union.
[b] FDX, fidaxomicin; MTZ, metronidazole; RIF, rifaximin; VAN, vancomycin. Overall results from FDX and VAN groups.

difficile isolates collected between 1983 and 2004 and reported all isolates susceptible to ≤0.25 μg/ml of fidaxomicin with a geometric mean MIC of 0.081 μg/ml. Karlowsky et al. (17) studied 208 Canadian strains of *C. difficile* and reported an MIC_{90} of 0.5 μg/ml for fidaxomicin (range, 0.06 to 1 μg/ml). Our study showed a fidaxomicin MIC_{90} of 0.25 μg/ml (range, 0.003 to 1 μg/ml) for 716 pretreatment isolates.

Our analysis of 725 strains from the PP populations of two

TABLE 5. Characteristics of strains from patients enrolled as metronidazole failures or with no prior metronidazole exposure (PP population)

Metronidazole failure	No. of patients	Antibiotic[a]	Geometric mean (range)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Yes	32	FDX	0.11 (0.03–0.5)	0.125	0.25
		VAN	1.0 (0.25–4)	1	2
		MTZ	0.48 (0.125–2)	0.5	1
`		RIF	0.03 (0.003–>256)	0.015	0.06
No	693	FDX	0.10 (0.003–1)	0.125	0.25
		VAN	0.97 (0.25–8)	1	2
		MTZ	0.48 (0.02–4)	0.5	1
		RIF	0.02 (0.003–>256)	0.015	0.125

[a] FDX, fidaxomicin; MTZ, metronidazole; RIF, rifaximin; VAN, vancomycin. Overall results from FDX and VAN groups.

phase III fidaxomicin versus vancomycin studies showed no relationship between the fidaxomicin MIC_{50}s and MIC_{90}s of baseline clinical isolates and clinical cure. Fidaxomicin MIC values were low at baseline, and resistance did not develop during the clinical trial. One strain in a patient who was clinically cured had an elevated MIC of 16 μg/ml at the time of recurrence. The vancomycin MIC_{90} of patients who failed therapy was 1 dilution higher (4 μg/ml) than the MIC_{90} of those patients who were cured (2 μg/ml). As the MIC_{50}s were the same and the geometric means were similar, this is unlikely to be a meaningful difference. Likewise, there were no notable differences in MIC_{50}s and MIC_{90}s for cognate antibiotics between recurrences and nonrecurrences (Table 2) (PP population).

MIC_{90}s for the agents tested were generally low (0.25 μg/ml fidaxomicin, 1 μg/ml metronidazole, and 2 μg/ml vancomycin) and were similar between REA groups. Within the BI group, the MIC_{90}s were generally 1 dilution higher for all agents (0.5 μg/ml fidaxomicin, 2 μg/ml metronidazole, and 2 μg/ml vancomycin). Vancomycin MICs of 4 μg/ml were found in some strains and were more prevalent in German isolates.

Johnson et al. (16) reported the use of vancomycin followed by rifaximin in the therapy of multiple recurrent *C. difficile* infections. Hecht et al. (14) reported a geometric mean rifaximin MIC of 0.009 for 110 *C. difficile* isolates but a range of 0.0038 to >16 μg/ml. There were 3 strains with rifaximin MICs of >256 μg/ml, of which two were isolated in Argentina and one in Chicago. More recently, Curry et al. (11) reported rifampin resistance in 173/470 (36.8%) of isolates from an epidemic *C. difficile* clone and that rifamycin preexposure was a risk factor for resistance. In our study, resistance to rifaximin (MIC > 256 μg/ml) was found in 7.9% of pretreatment strains, primarily within the BI group, the CF group, and the K group strains. No marked differences in susceptibilities of isolates were detected between the different geographic regions, except that there was more resistance to rifaximin (MIC > 256 μg/ml) in most of the United States (Northeast, Midwest, and West compared to the South) (MIC_{90} >256 μg/ml) than in Canada (MIC_{90}, 0.015 μg/ml), where rifaximin is not licensed. Resistance to rifaximin (MIC > 256 μg/ml) was also was observed in Germany and Italy, but not in the other European countries. Clinicians should be aware of the potential for resistance if rifaximin is used for treatment of *C. difficile* infection.

Reduced *C. difficile* susceptibility to metronidazole has been reported and can vary by ribotype. It has not been attributed to the presence of *nim* genes (12, 20). Since the mean metronidazole fecal concentration can vary from <0.25 to 9.5 μg/g, this raises concern about its continued potential clinical efficacy. In our study, there were no differences in MIC_{50} and MIC_{90} values for metronidazole between strains from patients enrolled as metronidazole failures and strains from patients who were not treated with metronidazole. Additionally, there were minimal differences in susceptibilities to other antibiotics, except for rifaximin, to which many strains from metronidazole failures were resistant.

Our study showed that there was no correlation between the MICs of baseline clinical isolates and clinical outcome of *C. difficile* infection. The MIC_{90}s were generally low for both fidaxomicin and vancomycin, but BI isolates generally had higher MICs.

ACKNOWLEDGMENTS

We thank Kerin Tyrrell, Vreni Merriam, Judee H. Knight, and Alice E. Goldstein for various forms of assistance.

This study was supported in part by grants from Optimer Pharmaceuticals, NIH SBIR grant 1 R43 AI 63692-01, and the U.S. Department of Veterans Affairs (to D.N.G.).

E.J.C.G. is on the advisory boards of Merck & Co., Optimer, Bayer Pharmaceuticals, BioK+, and Kindred Healthcare Corp. and the speakers' bureaus of Bayer Inc., Merck & Co., Sanofi Pasteur, and Forest Labs and has received research grants from Merck & Co., Schering-Plough Pharmaceuticals, Optimer Pharmaceuticals, Theravance Inc., Cubist, Pfizer Inc., Astellas Inc., Cerexa, Impex Pharmaceuticals, Novexel, Novartis, Clinical Microbiology Institute, Genzyme, Nanopacific Holdings Inc., Romark Laboratories LC, Viroxis Corp., Warner Chilcott, Avidbiotics Corp, GLSynthesis Inc., Immunome Inc., and Toltec Pharma LLC. D.M.C. and S.P.S. have no conflicts of interest. P.S. and F.B. are employees of Optimer Pharmaceuticals. D.N.G. holds patents for the treatment and prevention of *C. difficile* infection licensed to ViroPharma; is a consultant for ViroPharma, Optimer, Merck, Pfizer, Cubist, Actelion, Astellas, Medicines Co., and TheraDoc; and holds research grants from Merck, Eurofins Medinet, GOJO, Optimer, Sanofi-Pasteur, and ViroPharma.

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