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***Clostridium difficile* infection: update on emerging antibiotic treatment options and antibiotic resistance**

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Abstract

Clostridium difficile infection (CDI) is the most common cause of identifiable diarrhea in hospitalized patients. The incidence and severity of CDIs are increasing. The increased incidence and severity of the disease has sparked interest in the optimal treatment of CDI as well as the use of new therapies and drug discovery. Current treatment strategies are inadequate with decreased response rates to metronidazole, and high recurrence rates with the use of metronidazole and oral vancomycin. Although incidence rates continue to be low, *in vitro* resistance to antibiotics used for the treatment of CDI has been noted. Recently, important data has emerged on new anti-*C. difficile* antibiotics such as rifaximin, rifalazil, fidaxomicin, nitazoxanide, tigecycline and ramoplanin. The purpose of this review is to provide an update on the *in vitro* susceptibility and new antibiotic treatment options for CDI. This review will focus primarily on scientific studies published in the last 36 months in order to provide an up-to-date review on the topic.

Keywords

Clostridium difficile; fidaxomicin; nitazoxanide; rifaximin; treatment update

Clostridium difficile infection (CDI) is the most common cause of identifiable diarrhea in hospitalized patients. CDI is an evolving pathogen with high incidence and severity. Current treatment of CDI is evolving and a number of new antibiotic treatment options are available [1–3]. *In vitro* resistance to antibiotics used for the treatment of CDI continues to be low; however, resistance among certain strains has been identified. Recently, important data has emerged on new anti-*C. difficile* antibiotics such as rifaximin, rifalazil, fidaxomicin, nitazoxanide, tigecycline and ramoplanin. The purpose of this review is to provide an update on the *in vitro* susceptibility and new treatment options for CDI. The present article will focus on scientific studies published primarily in the last 36 months in order to provide an up-to-date review on the topic.

***In vitro* susceptibility & emerging resistance**

From 1983 to 2007 over 1500 strains from published studies have been used to assess the *in vitro* susceptibility of rifamycins, vancomycin, metronidazole, fidaxomicin, nitazoxanide, tigecycline and ramoplanin to *C. difficile* (Table 1) [4–20]. Susceptibility testing was primarily performed using the agar dilution method. A weighted mean for each antimicrobial (using the number of strains tested as the weighting measure) showed mean MIC₅₀ and MIC₉₀ values of rifamycin antibiotics less than 0.081 µg/ml. Weighted mean MIC values for metronidazole (MIC₅₀: 0.31 µg/ml; MIC₉₀: 1.50 µg/ml) and vancomycin (MIC₅₀: 0.73 µg/ml; MIC₉₀: 1.33 µg/ml) were similar. Weighted mean (MIC₅₀ and MIC₉₀) values for OPT-80, nitazoxanide, tigecycline and ramoplanin were all 0.4 µg/ml or less.

A number of *C. difficile* strains with decreased susceptibility have been reported. Pelaez *et al.* reported that 26 out of 415 (6.3%) tested strains had reduced susceptibility to metronidazole (defined as a MIC of 32 µg/ml or more) [6]. Twelve of these resistant isolates came from patients infected with HIV. The same study found 13 of 415 strains (3%) with reduced susceptibility to vancomycin (MIC range: 8–16 µg/ml). The highest rate of reduced susceptibility to vancomycin also occurred in HIV patients. Another study of 46 isolates from patients with stools positive for *C. difficile* toxin and diarrhea found one strain with decreased susceptibility to metronidazole (defined as a MIC >256 µg/ml) [12]. This isolate was from a child with Hirschsprung's disease status post-total colectomy and terminal ileum resection. Recent testing with the epidemic BI strain has also shown decreased susceptibility. A survey of approximately 200 isolates from Leeds, England, showed decreased susceptibility of metronidazole in 24.4% of *C. difficile* ribotype 001 cultured between 2005–2006 [21]. A BI/027 *C. difficile* strain with reduced susceptibility to vancomycin (MIC: 6 µg/ml) was reported in 2007 in England [16]. Furthermore, a recent study noted that the MIC₉₀ for metronidazole and vancomycin was two dilutions higher with BI/027 isolates (2 µg/ml) compared with non-BI isolates (0.5 µg/ml) [18]. A recent review has also provided an excellent summary of antibiotic resistance patterns in strains of *C. difficile* [22].

With CDI and drugs that concentrate in the gut, the concept of using antimicrobial breakpoints for resistance or susceptibility based on systemic drug concentrations may be inadequate [22]. More studies are needed to determine a physiologic breakpoint for enteric infectious diseases considering drug pharmacokinetics and pharmacodynamics. Colonic concentrations of active antibiotics should be related to the MIC of the organism in order to generate appropriate breakpoints for nonsystemic infections.

Update on treatment of CDI with metronidazole & oral vancomycin

A summary of randomized controlled trials with metronidazole or oral vancomycin compared with new or emerging therapies is presented in Table 2 [18,23–28]. Metronidazole and oral vancomycin have been the primary therapies for CDI since the late 1970s. Cumulative clinical data from trials in the late 1990s and early 2000s reported increasing treatment failure rates with metronidazole. A total of 294 out of 2226 (13.2%) patients with CDI failed with metronidazole compared with 24 out of 708 (3.4%) with vancomycin [29]. Recurrence of CDI was high regardless of treatment with metronidazole (20.2%) or oral vancomycin (18.4%). In 2007, Zar *et al.* published a prospective, double-blind study of metronidazole versus oral vancomycin for CDI [23]. Patients were stratified based on the severity of CDI. Patients were considered to have severe CDI if they displayed endoscopic evidence of colitis or were admitted to the intensive care unit. Patients were also considered severe if they had two or more of the following factors: age over 60 years, temperature greater than 38.3°C, albumin less than 2.5 mg/dl or white blood cell count greater than

15,000 cells/mm³. The cure rate was similar for patients given metronidazole (90%; n = 41) and oral vancomycin (98%; n = 40) for mild CDI. There was a significantly higher cure rate for severe patients treated with oral vancomycin (97%; n = 31) than metronidazole (76%; n = 38; p = 0.02). These results were similar to a Phase III comparator trial of tolevamer, a toxin-binding agent that was compared with metronidazole and oral vancomycin [30,31]. In this study, oral vancomycin was superior to metronidazole in patients with severe CDI. Similar results were also demonstrated in a retrospective, cohort, single-center study carried out by Le *et al.* [32]. European treatment and diagnostic guidelines for CDI have recently been published and incorporate these new findings [33,34].

New & emerging treatment options for *C. difficile* infection **Rifamycins**

Rifampin

Several agents in the rifamycin class have been investigated for the treatment of CDI (Table 3) [35–39]. Rifampin displays potent activity against *C. difficile* strains, however, emergence of resistance continues to be a concern. Resistance to rifampin may result from mutations in the *rpoB* gene, which encodes for the β -subunit of the *C. difficile* RNA polymerase [40]. In a recent survey of sequential *C. difficile* strains from hospitalized patients, 12 out of 163 isolates (7.4%) were resistant to rifampin (MIC >32 μ g/ml) using an E-test strip [41]. Resistance rates were much higher from a single center study in Pittsburgh (PA, USA) [42]. In this study, 173 out of 470 (36.8%) *C. difficile* strains displayed reduced susceptibility to rifampin. In sub-ana lysis, 167 out of 205 (81.5%) BI strains were resistant to rifampin. Clinical data supporting the use of rifampin in combination with metronidazole was studied versus metronidazole mono-therapy in CDI patients [43]. In this study, the median time to resolution of symptoms was similar in patients that received combination therapy compared with monotherapy (p = 0.74). The median time to first occurrence of relapse was also similar in patients receiving combination therapy compared with monotherapy (p = 0.23). This study was ended prematurely as an interim ana lysis indicated little chance of demonstrating superiority with combination therapy for CDI.

Rifaximin

Rifaximin, a nonabsorbable rifamycin, also displays potent activity against *C. difficile* strains. Rifaximin achieves high colonic concentrations greater than 8000 μ g/g and may spare enteric flora making it a potentially useful agent for a recurrence prevention strategy. The MIC₅₀ and MIC₉₀ of 110 isolates from multiple countries between 1983 and 2004 were 0.0075 and 0.015 μ g/ml, respectively [4]. Clinically, a small randomized study showed equivalence of rifaximin compared with oral vancomycin [44]. More recently, three case series have shown benefit for the use of rifaximin to prevent CDI recurrence. The first case series published in 2007 identified eight females with a history of four to eight episodes of recurrent CDI and multiple previous CDI treatment and dosing strategies [35]. Patients were given a 2-week course of rifaximin immediately after a successful treatment of oral vancomycin. After this 'rifaximin chaser' protocol, seven of eight (87.5%) females had no recurrence after a mean follow-up of 233 days. One female experienced recurrence 10 days after the end of rifaximin therapy, yet improved after a second course of 2-week rifaximin treatment. The rifaximin MIC for this *C. difficile* strain was 256 μ g/ml compared with the baseline MIC of 0.0078 μ g/ml prior to starting rifaximin therapy. In a follow-up case series, an additional six patients (five females and one male) with a history of three to eight episodes of recurrent CDI received a 2-week course of rifaximin, immediately after successful treatment with oral vancomycin [36]. Four patients were symptom-free at a follow-up period of 4–25 months, while two experienced treatment failure during the rifaximin therapy. Isolates for one patient displayed reduced susceptibility to rifaximin (MIC >256 μ g/ml). In another case series, five patients with a history of one to four episodes of

recurrent CDI received a rifaximin tapering regimen for a total of 28 days [37]. All five patients experienced no recurrence during the follow-up period of 54–398 days. A sixth patient received fixed-dose rifaximin for a total of 36 days. This patient continued to have symptoms after receiving rifaximin, and died due to cardiorespiratory failure. Unlike the previous case series, this series included both females and males, and these patients received rifaximin while symptomatic. From these case series, it appears that rifaximin may have an important role in preventing CDI recurrence; however, emergence of resistance may be a problem.

Rifalazil

Rifalazil, a newer benzoxazinorifamycin, is another potent rifamycin with fewer clinical data reported. The MIC₅₀ and MIC₉₀ for a total of 141 isolates range from 0.002 to 0.0075 µg/ml and 0.004 to 0.03 µg/ml, respectively [4,19]. In an animal-model study, hamsters with clindamycin-induced cecitis were administered rifalazil 20 mg/kg/day, vancomycin 50 mg/kg/day or vehicle – 0.8% DMSO by gavage [19]. The treatment was given as prophylaxis, at the time of clindamycin-induced cecitis, or as treatment given 2 h after infection. The hamsters were followed for a total of 34 days and assessed for recurrent CDI. Hamsters that received placebo treatment were in a moribund state within 4 h of infection. Hamsters that received either rifalazil or vancomycin remained symptom-free for the duration of treatment in the prophylaxis and treatment groups. After discontinuation of therapy, the majority of vancomycin-treated hamsters were in moribund state within 14–24 days after infection, while rifalazil-treated hamsters continued to have no signs of infection up to 34 days after infection. Based on this animal-model study, a 5-day course of rifalazil was superior compared with vancomycin for prevention of recurrent CDI.

Nitazoxanide—Nitazoxanide, a nitrothiazole benzamide, has activity against bacterial enteric pathogens and intestinal parasites [45]. Two thirds of the active drug is excreted in the feces. Two studies conducted *in vitro* susceptibility testing for nitazoxanide in 125 isolates. The MIC₅₀ and MIC₉₀ ranged from 0.06 to 0.25 µg/ml and 0.125 to 0.5 µg/ml, respectively. Two randomized trials and a retrospective cohort study have assessed the clinical effectiveness of nitazoxanide for the treatment of CDI. Musher *et al.* conducted a prospective, double blind study comparing nitazoxanide with metronidazole in patients with CDI [24]. Clinical response rate after 7 days of treatment was 89.5% (n = 76) with nitazoxanide given for 7 or 10 days and 82.4% (n = 34) with metronidazole given for 10 days (difference of 7.1%; 95% CI: -7–25.5). An open-label study assessed response rates of nitazoxanide given for 10 days in 35 CDI patients who had failed metronidazole therapy [46]. A total of 54% of patients responded to nitazoxanide therapy with an additional four patients who either failed initial treatment or had recurrence, responding to a second course of nitazoxanide (overall response rate: 66%). A prospective, double blind study was conducted comparing nitazoxanide with oral vancomycin in patients with diarrhea, positive for *C. difficile* toxin via enzyme immunoassay and at least one of fever or leukocytosis [25]. At the end of treatment, response rate was 74% (n = 27) in the vancomycin group and 77% (n = 23) in the nitazoxanide group. Overall, nitazoxanide was well tolerated in these studies with no serious adverse events reported.

Tigecycline—Tigecycline is a glycycline antibiotic and a derivative of minocycline. Tigecycline undergoes minimal metabolism with the majority of unchanged, active drug excreted in the feces [47]. Fecal concentrations range from 3.0–14.1 µg/g stool (mean: 6.0 µg/g; median: 5.6 µg/g) [48]. Tigecycline decreases Lactobacilli and Bifidobacteria in the stool with minimal impact on *Bacteroides* species. *In vitro* susceptibility of tigecycline to *C. difficile* based on three published studies with 215 total isolates showed a MIC₅₀ and MIC₉₀ range of 0.032 to 0.125 µg/ml and 0.032 to 0.25 µg/ml, respectively [4,7,9]. Clinical data for

treatment of CDI with tigecycline stems from a case series of four patients with severe refractory CDI (two males and two females), treated with standard therapy followed by tigecycline in three patients and as primary therapy in one patient [38]. Three patients had received standard metronidazole, vancomycin or combination metronidazole and vancomycin treatment from 27 to 57 days before the addition of tigecycline. Duration of therapy varied in the four patients. Symptomatic relief was reported 3–7 days after tigecycline initiation and all four patients reported no relapse in 3 months of follow-up. These results will require verification before the use of tigecycline for refractory CDI can be recommended.

Fidaxomicin (FDX, OPT-80)—One of the newest agents currently completing Phase III trials is fidaxomicin, formerly known as OPT-80 and PAR-101. Fidaxomicin is a narrow spectrum macrocyclic antibiotic with potent activity against *C. difficile* but limited activity against other Gram-positive bacteria [13,18]. The MIC₅₀ and MIC₉₀ from 415 isolates ranged from ≤ 0.016 to 0.25 $\mu\text{g/ml}$ and 0.125 to 0.5 $\mu\text{g/ml}$, respectively. Citron *et al.* stratified 38 isolates based on strain type, in which the fidaxomicin MIC₉₀ was the same for BI/027 and non-BI strains (0.125 $\mu\text{g/ml}$) [18].

The impact of fidaxomicin on the human gastrointestinal microbiota in terms of *Bacteroides* and vancomycin-resistant *Enterococci* (VRE) species has been assessed in two studies [49,50]. In a prospective, open label study, *Bacteroides* count increased from baseline after 10 days of fidaxomicin therapy, while *Bacteroides* count decreased with vancomycin treatment [49]. Nerandzic *et al.* reported that 63% (n = 142) of patients given fidaxomicin had greater than 5 log₁₀ *Bacteroides* spp./g of stool compared with 13% (n = 160) of patients given oral vancomycin (p = 0.004) [50]. There was a 7% (n = 115) acquisition of VRE in the fidaxomicin group as compared with 33% (n = 160) in the vancomycin group in patients with stool culture negative for VRE at baseline (p < 0.001).

In a prospective, open-label, multicenter, dose-ranging, Phase II study of patients with mild-to-moderate CDI, the overall cure rate with fidaxomicin was 91% (n = 45) with a dose-dependent response rate observed [26]. The overall cure rate was 79% (n = 14) in patients with BI/027 strains and 95% (n = 22) with non-BI strains (p = not significant) [18]. In a prospective, randomized, multicenter Phase III trial of oral vancomycin compared with fidaxomicin, outcomes were stratified based on strain type [28]. The cure rate was significantly lower in the BI/027 group (84.7%; n = 137) compared with the non-BI group (95.5%; n = 245; p = 0.001), regardless of fidaxomicin or vancomycin treatment. In fidaxomicin-treated patients, the cure rate was 86.2% (n = 65) in the BI/027 group and 96.6% (n = 119) in the non-BI group (p = 0.013). In the vancomycin-treated patients, the cure rate was lower in the BI/027 group than in the non-BI group (p = 0.037).

In the Phase III trial, the recurrence rate, defined as diarrheal and positive toxin recurrence within 28 days after the end of therapy with fidaxomicin or vancomycin, was also assessed [27]. Overall, recurrence rates were lower with fidaxomicin (13.3%; n = 211) compared with vancomycin treatment (53%; n = 221; p = 0.04). However, in patients infected with the BI/NAP1 strain, there was no significant difference in recurrence rate between fidaxomicin- and vancomycin-treated patients [28]. In the Phase III clinical trial, fidaxomicin 200 mg every 12 h and vancomycin 125 mg every 6 h had a similar safety profile [51]. Any adverse event was reported in 62.3% (n = 300) in the fidaxomicin group and 60.4% of patients (n = 323) in the vancomycin group. Approximately 25% of patients in each group experienced a serious adverse event with few attributable to the study drug. The three most common adverse effects in both groups were nausea, hypokalemia and headache. All-cause mortality was 5.3% in the fidaxomicin group and 6.5% in the vancomycin group.

Expert commentary

Recent randomized controlled studies have confirmed the superiority of oral vancomycin over metronidazole for the treatment of severe CDI. Treatment of CDI based on severity has been incorporated into recent European guidelines [33]. Decreasing response rates to metronidazole and high recurrence rates with metronidazole and oral vancomycin demonstrate the need for new antibacterial agents. Nitazoxanide has shown comparable results to metronidazole and oral vancomycin in two separate randomized controlled studies. Case series have shown positive results with the use of rifaximin as a chaser regimen after conventional therapy for the prevention of recurrent CDI, but prospective clinical trials are needed to evaluate the use of rifaximin and rifalazil as therapy for primary or recurrent CDI episodes. Fidaxomicin displayed positive results in the Phase III study versus oral vancomycin with decreased recurrence rates observed in patients infected with non-BI strains. Surprisingly, recurrence rates with the two antibiotics were similar for patients infected with the BI strain. The other major challenge with CDI is patients unable to take oral medications due to ileus or toxic megacolon. In these difficult cases, intravenous metronidazole is often given in conjunction with vancomycin administered by enema. The case series of tigecycline offers a potential new alternative for intravenous therapy and the treatment of CDI. This small case series will require confirmation prior to large-scale use in clinical practice. The use of nonantibiotic therapies such as toxin binders (tolevamer), monoclonal antibodies and stool transplantation with standard and emerging antibiotic therapies will require intense research efforts over the next 5 years.

Five-year view

In the future, defining severity of CDI and the role of metronidazole will be essential. No antibiotic is likely to be superior to oral vancomycin for the treatment of acute infections; however, an agent that shows decreased recurrence rates of CDI would be a major advance in the treatment of the disease. The drugs that show most promise based on clinical trials to date include nitazoxanide, rifaximin and fidaxomicin.

Key issues

- The incidence and severity of *Clostridium difficile* infections (CDIs) are increasing.
- Current optimal treatment strategies are lacking with decreased response rates to metronidazole and high recurrence rates with the use of metronidazole or oral vancomycin.
- A number of *C. difficile* strains with decreased susceptibility to metronidazole have been reported.
- A prospective, double-blind study published in 2007 of metronidazole versus oral vancomycin for CDI demonstrated superiority of oral vancomycin for the treatment of severe CDI. Similar results were observed in subsequent randomized controlled trials and observational studies.
- Use of rifaximin as a chaser regimen after conventional therapy has shown low recurrence rates in multiple case series. Emergence of resistance is a concern. Nitazoxanide has shown equivalence to metronidazole and oral vancomycin in two separate randomized controlled trials.
- Intravenous tigecycline was effective for refractory CDI in a small case series of four patients.

- Fidaxomicin was equivalent to oral vancomycin in a Phase III study. Recurrence rates were lower for fidaxomicin in patients infected with non-BI strains but similar for patients infected with BI strains.

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[PubMed: 18385603] [Case series of five patients with a history of one to four episodes of recurrent CDI who received a rifaximin tapering regimen for a total of 28 days. None of the five patients experienced any recurrence during the follow-up period of 54–398 days. A sixth patient received fixed-dose rifaximin for a total of 36 days but continued to have symptoms. This case series adds to previous case series demonstrating a potential efficacy of rifaximin to decrease the recurrence rate of CDI.]

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Table 1

Antibiotic susceptibility of *Clostridium difficile* isolates

Author	Location	Year(s)	Isolates (n)	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)	Range (µg/ml)	Ref.
<i>Metronidazole</i>							
Hecht <i>et al.</i>	Various	1983–2004	110	0.125	0.25	0.025–0.5	[4]
Swanson <i>et al.</i>	Various	1990	15	0.25	0.5	0.12–0.5	[5]
Pelaez <i>et al.</i>	Spain	1993–2000	415	0.5	4	0.016–>32	[6]
Edlund <i>et al.</i>	Sweden	1998	50	0.125	0.25	0.125–0.25	[7]
McVay and Rolfe	Various	2000	15	0.25	0.5	0.13–0.50	[8]
Betriu <i>et al.</i>	Spain	2001	55	0.5	1	≤0.06–1	[9]
Citron <i>et al.</i>	USA	2003	18	0.5	1	0.25–1	[10]
Finegold <i>et al.</i>	USA (CA)	2003	72	0.5	1	0.25–2	[11]
Bishara <i>et al.</i>	Israel	2003–2004	46	0.032	0.125	0.016–0.5	[12]
Credito and Appelbaum	USA (MI)	2004	21	0.25	0.5	≤0.125–0.5	[13]
Finegold <i>et al.</i>	USA (CA)	2004	23	0.25	0.5	0.25–1	[14]
Barbut <i>et al.</i>	Europe	2005	349	0.064	0.125	0.023–0.50	[15]
Sundram <i>et al.</i>	England	2006–2007	39	0.12	0.75	NR	[16]
Karlowsky <i>et al.</i>	Canada (Manitoba)	2007	208	0.5	1	0.25–4	[17]
Citron <i>et al.</i>	USA (various), BI strain	2004–2005	16	NR	2	0.5–2	[18]
Citron <i>et al.</i>	USA (various), non-BI	2004–2005	22	NR	0.5	0.25–1	[18]
Total		1983–2007	1474	0.31	1.50	0.016–>32	
<i>Vancomycin</i>							
Hecht <i>et al.</i>	Various	1983–2004	110	1	1	0.06–4	[4]
Swanson <i>et al.</i>	Various	1990	15	0.5	1	0.5–1	[5]
Bishara <i>et al.</i>	Israel	2003–2004	46	0.023	1	0.016–1.5	[12]
Credito and Appelbaum	USA (MI)	2004	21	1	2	0.5–2	[13]
Pelaez <i>et al.</i>	Spain	1993–2000	415	1	2	0.016–16	[6]
McVay and Rolfe	Various	2000	15	0.5	0.5	0.13–1	[8]
Citron <i>et al.</i>	USA	2003	18	1	2	0.5–4	[10]
Finegold <i>et al.</i>	USA (CA)	2003	72	1	2	0.5–4	[11]

Author	Location	Year(s)	Isolates (n)	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)	Range (µg/ml)	Ref.
Finegold <i>et al.</i>	USA (CA)	2004	23	1	2	0.5–4	[14]
Barbut <i>et al.</i>	Europe	2005	349	0.5	0.75	0.25–2	[15]
Sundram <i>et al.</i>	England	2006–2007	39	0.38	2	NR	[16]
Karlowsky <i>et al.</i>	Canada (Manitoba)	2007	208	0.5	1	0.5–4	[17]
Citron <i>et al.</i>	USA (various), BI strain	2004–2005	16	NR	2	0.5–2	[18]
Citron <i>et al.</i>	USA (various), non-BI	2004–2005	22	NR	0.5	0.25–1	[18]
Total		1983–2007	1369	0.73	1.33	0.016–16	
<i>Nitazoxanide</i>							
Hecht <i>et al.</i>	Various	1983–2004	110	0.06	0.125	0.03–0.5	[4]
McVay and Rolfe	Various	2000	15	0.25	0.5	0.13–1	[8]
Total		1983–2004	125	0.083	0.17	0.03–1	
<i>OPT-80</i>							
Swanson <i>et al.</i>	Various	1990	15	0.25	0.25	0.12–0.25	[5]
Hecht <i>et al.</i>	Various	1983–2004	110	0.125	0.125	0.015–0.25	[4]
Finegold <i>et al.</i>	USA (CA)	2004	23	0.12	0.25	0.06–2	[14]
Credito and Appelbaum	USA (MI)	2004	21	≤0.016	0.125	≤0.016–0.25	[13]
Karlowsky <i>et al.</i>	Canada (Manitoba)	2007	208	0.25	0.5	0.06–1	[17]
Citron <i>et al.</i>	USA (various), BI strain	2004–2005	16	NR	0.125	0.03–0.25	[18]
Citron <i>et al.</i>	USA (various), non-BI	2004–2005	22	NR	0.125	≤0.008–0.25	[18]
Total		1983–2007	415	0.19	0.37	<0.008–2	
<i>Rifampin</i>							
Bishara <i>et al.</i>	Israel	2003–2004	46	0.002	0.19	0.002–0.25	[12]
Karlowsky <i>et al.</i>	Canada (Manitoba)	2007	208	0.015	0.015	0.002–>2	[17]
Total		2003–2007	254	0.013	0.047	0.002–>2	
<i>Rifaximin</i>							
Hecht <i>et al.</i>	Various	1983–2004	110	0.0075	0.015	0.0038–>16	[4]
Jiang <i>et al.</i>	USA (TX)	2006–2007	163	<0.03	0.125	<0.01–>32	[41]
Total		1983–2007	273	0.021	0.081	0.0038–>32	
<i>Rifalazil</i>							

Author	Location	Year(s)	Isolates (n)	MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)	Range (µg/ml)	Ref.
Hecht <i>et al.</i>	Various	1983–2004	110	0.0075	0.03	0.0019–>16	[4]
Anton <i>et al.</i>	USA (MA)	2004	31	0.002	0.004	NR	[19]
Total		1983–2004	141	0.006	0.024	0.0019–>16	
<i>Ramoplanin</i>							
Hecht <i>et al.</i>	Various	1983–2004	110	0.25	0.5	0.06–0.5	[4]
Pelaez <i>et al.</i>	Spain	1994–2002	105	0.25	0.25	0.03–0.5	[20]
Finigold <i>et al.</i>	USA (CA)	2003	72	0.5	0.5	0.25–1	[11]
Citron <i>et al.</i>	USA	2003	18	0.25	0.25	0.25–0.5	[10]
Total		1983–2004	305	0.31	0.40	0.03–1	
<i>Tigecycline</i>							
Hecht <i>et al.</i>	Various	1983–2004	110	0.125	0.25	0.06–1	[4]
Edlund <i>et al.</i>	Sweden	1998	50	0.032	0.032	0.016–0.032	[7]
Betriu <i>et al.</i>	Spain	2001	55	≤0.06	0.125	≤0.06– 2	[9]
Total		1983–2004	215	0.087	0.167	0.016–2	

Total: refers to a weighted mean for each antimicrobial using the number of strains tested as the weighting measure.

NR: Not reported.

Table 2
Summary of randomized controlled trials investigating antibacterial agents for the treatment of *Clostridium difficile* infection.

Patients (n)	Severity stratification	Treatment	Treatment (days)	EOT response (%)	Recurrence (%)	Sustained response (%)	p < 0.05
<i>Double blind</i> [23]							
41	Mild	Metronidazole 250 mg q6h	10	90	8	82	No
40	Mild	Vancomycin (liquid) 125 mg q6h	10	98	5	93	
38	Severe	Metronidazole 250 mg q6h	10	76	21	55	Yes
31	Severe	Vancomycin (liquid) 125 mg q6h	10	97	10	87	
<i>Double blind</i> [24]							
34	Not done	Metronidazole 250 mg q6h	10	82	24	58	No
40		Nitazoxanide 500 mg q12h	7	90	23	67	
36		Nitazoxanide 500 mg q12h	10	89	14	75	
<i>Double blind</i> [25]							
18	Not done	Nitazoxanide 500 mg q12h	10	77	5	72	No
23		Vancomycin 125 mg q6h	10	74	7	67	
<i>Open label</i> [18,26]							
14	Mild-moderate	Fidaxomicin 50 mg q12h	10	71	8	63	No
15	Mild-moderate	Fidaxomicin 100 mg q12h	10	80	0	80	
16	Mild-moderate	Fidaxomicin 200 mg q12h	10	94	6	88	
6	Non-BI strain	Fidaxomicin 50 mg q12h	10	100	17	83	
9	Non-BI strain	Fidaxomicin 100 mg q12h	10	89	0	89	
7	Non-BI strain	Fidaxomicin 200 mg q12h	10	100	14	86	
5	BI strain	Fidaxomicin 50 mg q12h	10	60	0	60	
4	BI strain	Fidaxomicin 100 mg q12h	10	75	0	75	
5	BI strain	Fidaxomicin 200 mg q12h	10	100	0	100	
<i>Multicenter, double blind</i> [27,28]							
65	BI strain	Fidaxomicin 200 mg q12h	10	86	24	62	No
72	BI strain	Vancomycin 125 mg q6h	10	85	24	61	
119	Non-BI strain	Fidaxomicin 200 mg q12h	10	97	8	89	Yes
126	Non-BI strain	Vancomycin 125 mg q6h	10	94	26	68	

Sustained response defined as EOT success minus recurrence.

EOT: End of therapy; q6h: Every 6 h; q12h: Every 12 h.

Summary of observational studies that have investigated new and emerging antibiotics for *Clostridium difficile* infection.

Table 3

Case reports/series	Patients (n)	Treatment	Treatment (days)	Outcomes	Ref.
Eight females with four to eight episodes of recurrent CDI received rifaximin after asymptomatic with vancomycin treatment	6	Rifaximin 400 mg q12h	14	Seven of eight patients without recurrence after 233 days of mean follow-up	[35]
	1	Rifaximin 200 mg q12h	14		
	1	Rifaximin 200 mg q8h	14		
Six patients (five females, one male) with three to eight episodes of recurrent CDI received rifaximin after asymptomatic with vancomycin treatment	6	Rifaximin 400 mg q12h	14	Four of six patients without recurrence at follow-up period of 4–26 months	[36]
Six patients (four females, two males) with one to four episodes of recurrent CDI received rifaximin after conventional therapy	5	Rifaximin taper: 400 mg q8h then 200 mg q8h	28	Five of six patients without recurrence at follow-up period of 54–398 days	[37]
	1	Rifaximin 400 mg q8h	36		
58-year-old female with recurrent CDI; renal failure on peritoneal dialysis treated with nitazoxanide and probiotics	1	Nitazoxanide 500 mg q12h	42	No recurrence at 4 months follow-up	[39]
Four patients (two females, two males) with severe refractory CDI	1	Tigecycline + vancomycin	21	Four of four patients responded to tigecycline	[38]
	1	Tigecycline	15		
	1	Tigecycline followed by vancomycin	7 followed by 28		
	1	Tigecycline	24 days followed by pulse therapy		

CDI: *Clostridium difficile* infection; q6h: Every 6 h; q8h: Every 8 h; q12h: Every 12 h.