Emerging therapies for Clostridium difficile infection – focus on fidaxomicin

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Abstract: The epidemiology of Clostridium difficile infections (CDI) has evolved during the last decades, with an increase in the reported incidence, severity of cases, and rate of mortality and relapses. These increases have primarily affected some special populations including the elderly, patients requiring concomitant antibiotic therapy, patients with renal failure, and patients with cancer. Until recently, the treatment of CDI was limited to either metronidazole or vancomycin. New therapeutic options have emerged to address the shortcomings of current antibiotic therapy. Fidaxomicin stands out as the first-in-class oral macrocyclic antibiotic with targeted activity against C. difficile and minimal collateral damage on the normal colonic flora. Fidaxomicin has demonstrated performance not inferior to what is considered the “gold standard” available therapy for CDI, vancomycin, in two separate Phase III clinical trials, but with significant advantages, including fewer recurrences and higher rates of sustained clinical cures. Fidaxomicin constitutes an important development in targeted antibiotic therapy for CDI and must be considered as a first-line agent for patients with risk factors known to portend relapse and severe infection.

Keywords: fidaxomicin, Clostridium difficile-associated diarrhea, CDAD, Clostridium difficile infection (CDI), vancomycin, metronidazole

Introduction

Clostridium difficile, a gram-positive anaerobic spore-forming bacillus, has been implicated in 20% to 30% of cases with antibiotic-associated diarrhea; in 50% to 70% of those with antibiotic-associated colitis; and in more than 90% of those with antibiotic-associated pseudomembranous colitis.1 Collectively, these conditions are commonly known as C. difficile infections (CDI).2–4 In 2009, over 336,000 cases of CDI were reported in the United States.5 In nature, C. difficile exists as a spore and it is postulated that in vivo sporulation to the vegetative or toxin-producing form of this organism is suppressed by the presence of normal intestinal microflora. CDI results from a combination of disruption of the normal intestinal microflora and sporulation, and the overgrowth of native or newly acquired C. difficile spores with an associated production of clostridial glycosylating toxins.6,7 Because antibiotics alter the intestinal microflora, antibiotic administration is the most common predisposing factor for acquiring CDI.1 Other proposed mechanisms by which antibiotics might further influence the risk of CDI include alteration of colonic adhesion of C. difficile and induction of toxin production.6,9

The epidemiology and clinical presentation of CDI has changed during the last decades with an increased incidence of cases; more severe presentations; more frequently
reported disease in community settings; and higher rates of refractory, relapsing disease. Rising incidence of CDI and increasing rates of complicated disease with limited therapeutic options have prompted research for new agents to treat this condition. Because there are no randomized controlled trials evaluating the management of patients with severe complicated or recurrent disease, these entities remain a challenge. Recent efforts have focused on issues such as reducing the risk of treatment failures and recurrences; reducing treatment-related systemic adverse effects; preserving the intestinal microbiota; and optimizing humoral immunity. The aims of this article are to review treatment options for CDI and to describe recent therapeutic advancements in management with an emphasis on the newest available agent approved for treatment of CDI, fidaxomicin.

Patients with classical manifestations of CDI such as diarrhea, abdominal pain, nausea, vomiting, and a positive diagnostic test for *C. difficile* should receive treatment. Familiarity with the basic CDI definitions can help treating physicians select the appropriate pharmacologic intervention in given cases based upon severity of the disease (Table 1). These definitions are based on expert opinion, as published in the most current guidelines for the management of CDI. The initial step in treating CDI, as recommended in the guidelines, is the withdrawal of any offending antibiotic known to be associated with the development of the disease. Unfortunately, in many clinical situations, patients require concomitant systemic antimicrobials for concurrent infection(s), resulting in higher rates of treatment failures and recurrent disease.

### Antibiotic treatment options for CDI

Until the US Food and Drug Administration (FDA) approved fidaxomicin in May 2011, vancomycin was the only FDA approved agent for the treatment of CDI. The current published CDI guidelines, developed prior to the release of fidaxomicin, advocate for treatment with oral metronidazole in cases of mild to moderate disease, oral vancomycin for serious CDI, and combination therapy with enteral vancomycin and intravenous metronidazole in cases of ileus or toxic megacolon (Table 1). New and alternative pharmacological regimens used for the management of CDI are outlined in Table 2.

### Metronidazole

Widespread use of metronidazole over vancomycin was advocated in the 1995 Healthcare Infection Control Practices Advisory Committee guidelines in an effort to reduce the spread of vancomycin-resistant *Enterococci* (VRE). However, acquisition of VRE may arise from exposure to either metronidazole or vancomycin. Recent reports show declining efficacy of metronidazole. Rates of treatment failure have increased from ∼3% before the year 2000 to >18% after 2000. Although treatment failures may be related to reduced susceptibility of *C. difficile* strains, treatment failures could as well be related to inadequate fecal concentrations of metronidazole.

Metronidazole remains a widely used agent for CDI treatment given its inexpensive cost and availability. Two randomized trials, however, have shown vancomycin to be superior to metronidazole for severe, but not for mild to moderate, CDI disease. Limitations of metronidazole include side effects of nausea, metallic taste, disulfiram reactions with alcohol use, dose-dependent irreversible peripheral neuropathy, and inferior efficacy in severe CDI.

### Vancomycin

Until 2011, oral vancomycin was the only FDA approved treatment for CDI, making it the only comparator in

| Table 1 | Definitions and recommendations for the treatment of *Clostridium difficile* infection |
|---------|---------------------------------------------------------------------------------|
| **Clinical definition** | **Clinical and laboratory data** | **Recommended therapy** |
| Initial episode, mild or moderate | Leukocytosis with WBC $\leq$ 15,000 cells/μL, serum creatinine level $\leq$ 1.5 times the baseline level. | Metronidazole 500 mg PO every 8 hours for 10–14 days. |
| Initial episode, severe | Leukocytosis with WBC $\geq$ 15,000 cells/μL, serum creatinine level $\geq$ 1.5 times the baseline level. | Vancomycin 125 mg PO every 6 hours for 10–14 days. |
| Initial episode, severe complicated | Hypotension or shock, ileus, megacolon. | Vancomycin 500 mg PO/NG tube every 6 hours, plus metronidazole 500 mg IV every 8 hours. If complete ileus, consider vancomycin rectal enemas. Same as for initial episode. |
| First recurrence | – | Vancomycin tapered and/or pulse regimen. |
| Second recurrence | – | |

Adapted with permission from Cohen SH, Gerding DN, Johnson S, et al; for Society for Healthcare Epidemiology of America, Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infections in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431–455.

**Abbreviations:** WBC, white blood cell; PO, orally; NG, nasogastric; IV, intravenously.
Table 2 Available antibiotics and investigational new agents for the management of CDI

| Agent      | Dose                                                                 | Relative efficacy | Recurrence risk | Resistance in clinical isolates | Cost/total treatment costs | Adverse events                                                                 | Comments                                                                                                                                 |
|------------|----------------------------------------------------------------------|-------------------|-----------------|--------------------------------|---------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Fidaxomicin| 200 mg PO BID × 10 days.                                             | +++               | +               | Not reported.                  | $$$$/$$$                  | Abdominal pain, nausea, vomiting, anemia, neutropenia bowel obstruction, and GI hemorrhage. | FDA approved for CDI. First-in-class oral macrocylic antibiotic with targeted bactericidal activity against C. difficile and minimal impact on normal flora. |
| Vancomycin | 125 mg PO QID × 10–14 days or “taper/pulse” for recurrence: 125 mg PO QID × 10–14 days, then 125 mg PO BID per day × 1 week, then 125 mg PO every 2 or 3 days for 2–8 weeks. | +++               | ++              | Not reported.                  | $$$$$/$$$$$               | Nausea, not absorbed so systemic symptoms unlikely.                             | FDA approved for CDI. Potential for resistance induction in other clinically important pathogens.                                     |
| Metronidazole | 500 mg PO TID × 10 days or 250 mg PO QID × 10 days.            | ++                | ++              | Increased MICs noted in some studies. | $/$                       | Nausea, neuropathy, abnormal taste in mouth.                                    | Not FDA approved for CDI. Increased reports of treatment failures and slow response, less effective in severe CDI.                     |
| Nitazoxanide | 500 mg PO BID × 10 days.                                           | ++                | ++              | Not reported.                  | $                        | Nausea, diarrhea, abdominal pain.                                              | Not FDA approved.                                                                                                                         |
| Rifaximin  | 400 mg PO TID × 10 days or “chaser” regimen 400 mg PO BID × 14 days. | ++                | +?              | Potential for development of high level resistance. | $$$$/$$$$$               | Headaches, abdominal pain, nausea, flatulence, not absorbed.                  | Not FDA approved for CDI used primarily as post-vancomycin.                                                                             |
| Teicoplanin | 400 mg PO BID × 10 days.                                           | +++               | ++              | Not reported.                  | NA in US                  | Not absorbed so systemic symptoms unlikely.                                    | Not FDA approved for CDI similar results to vancomycin.                                                                                  |
| Tigecycline | 50 mg IV every 12 hours × 10 days.                                  | ++?               | ?               | Not reported.                  | $$$$$                    | Nausea, vomiting, diarrhea.                                                   | Not FDA approved for CDI. Limited case reports of treatment success and failures.                                                        |
| Bacitracin  | 25,000 units PO QID × 10 days.                                     | +                 | +++             | Increased resistance noted.   | $                        | Minimal absorbed, poor taste.                                                 | Not FDA approved for CDI. Limited efficacy secondary to resistance.                                                                      |
| Fusidic acid| 250 mg PO TID × 10 days.                                           | ++                | ++              | Reported to develop in vivo resistance. | NA in US                  | Nausea, vomiting, epigastric pain, anorexia.                                   | Not FDA approved for CDI. Concern about use as a single agent.                                                                         |

Investigational new agents

| Agent          | Comments                                                                                                                                 |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Ramoplanin     | Under investigation (Phase II) for the treatment of CDI. Lipoglycodepsipeptide with spectrum activity similar to vancomycin but consistently more potent. |
| Cadazolid      | Hybrid oxazolidinone-quinolone antibiotic. Currently in Phase II (NCT01222702).                                                        |
| CB-183,315     | Narrow spectrum, gram-positive lipopeptide antibiotic in Phase III development status.                                                  |

Adapted with permission from Cornily OA. Current and emerging management options for Clostridium difficile infection: what is the role of fidaxomicin? Clin Microbiol Infect. 2012;18 Suppl 6:34–35 and Venugopal AA, Johnson S. Current state of Clostridium difficile treatment options. Clin Infect Dis. 2012;55 Suppl 2:S71–S76.

Note: Not enough data present to give accurate quantitation.

Abbreviations: CDI, Clostridium difficile infection; PO, orally; BID, twice a day; GI, gastrointestinal; FDA, US Food and Drug Administration; QID, four times a day; VRE, vancomycin-resistant Enterococci; TID, three times a day; MIC, minimal inhibitory concentration; NA, not applicable; IV, intravenous.
studies evaluating new agents for this indication.\textsuperscript{17,22,23} Advantages over metronidazole include high intraluminal concentrations with low levels of systemic absorption after oral administration and higher efficacy for treatment of primary episodes of CDI, especially in severe cases. Limits to its widespread use include high levels of relapse (25\%–35\% in four recent clinical trials), acquisition cost, and concerns for bacterial colonization and overgrowth of \textit{Staphylococcus} and \textit{Enterococcus}, including vancomycin-resistant strains.\textsuperscript{1,16,17,22–24} Multiple treatment strategies for management of recurrent CDI including use of higher doses and/or extended duration of vancomycin therapy have not shown improved clinical outcomes. Prolonged vancomycin given either as a tapered regimen or in pulsed dosing, postulated to allow recovery of intestinal microbiota while inhibiting germination of residual spores, have shown higher rates of cure and fewer recurrences compared to standard 10–14 day regimens.\textsuperscript{25,26}

\textbf{Fidaxomicin, a new therapeutic alternative for CDI}

Fidaxomicin, a first-in-class 18-membered macrocyclic antibiopic previously known as OPT-80, PAR-101, and difimicin was approved in May 2011 by the FDA for the treatment of adults with CDI.\textsuperscript{27–29}

\textbf{Mechanism of action}

Fidaxomicin is a bactericidal antibiotic that has a lower in vitro minimum inhibitory concentration (MIC) against \textit{C. difficile} strains, including NAP1/B1/027, than does metronidazole or vancomycin.\textsuperscript{30} It has very limited activity against other bowel flora and modest activity against \textit{Staphylococcus} spp. and \textit{Enterococcus}, including vancomycin-resistant \textit{Enterococcus}.\textsuperscript{31} It inhibits bacterial protein transcription by interfering with ribonucleic acid (RNA) polymerase, producing a rapid suppression of RNA synthesis, followed by an inhibition of protein synthesis and, ultimately, deoxyribonucleic acid synthesis.\textsuperscript{32–34} It acts at a different site and step of RNA synthesis than rifamycins, and thus far no overlapping antibiotic resistance has been described.\textsuperscript{34–36} Fidaxomicin is more potent at suppressing clostridial RNA polymerase than against other bacterial species.

\textbf{Efficacy studies and comparative analysis}

Two large, concurrently run, double-blind randomized noninferiority trials (OPT 101.1.C.003 and OPT 101.1.C.004), compared fidaxomicin to vancomycin in the treatment of CDI.\textsuperscript{22,23} Patients with a new onset or first recurrence of CDI within 3 months prior to randomization were assigned to receive either fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The primary endpoint of a noninferior clinical cure (resolution of CDI symptoms and no need for further therapy at the end of therapy) between the two treatment arms was met in both the modified intention-to-treat analysis and the per-protocol analysis (Figure 1). The analysis of secondary endpoints of CDI recurrence and global cure (clinical cure and no recurrence of disease at 28 days after completion of study drug therapy) showed that significantly fewer patients in the fidaxomicin group than in the vancomycin group had recurrence of CDI (Figure 2), and consequently, those treated with fidaxomicin
had a statistically significant improved rate of global cure. Although the numbers of subjects who were infected with NAP1/BI/027 strains in these trials were small, the rates of cure and global cure in the per-protocol analysis were not significantly different in those treated with fidaxomicin than in those treated with vancomycin.

A post hoc exploratory intent-to-treat time-to-event meta-analysis of the combined data from these two trials was performed, to allow increased power with 1164 total subjects, using a fixed effects meta-analysis and Cox regression models. There was no evidence found of heterogeneity in the primary and secondary outcomes in either the modified intention-to-treat or per-protocol populations ($P > 0.3$). Overall, the results of this analysis again demonstrated noninferiority of fidaxomicin when compared to vancomycin for clinical cure and superiority of fidaxomicin over vancomycin in reduction of recurrence and global cure ($P < 0.0001$). When compared to vancomycin, treatment with fidaxomicin was associated with an overall 40% reduction in persistent diarrhea, recurrence, or death through the 40-day study period ($P < 0.001$). There was no evidence to show that the significant differences in relapse and global cure in the fidaxomicin- compared to the vancomycin-treated subjects was altered according to disease severity, prior history of CDI, previous antibiotic therapy for CDI, inpatient/outpatient status, age, or baseline albumin or creatinine levels. Patients treated with fidaxomicin for CDI due to non-NAP1/BI/027 strains and with hemoglobin levels higher than 10 g/dL experienced a greater benefit than those infected by NAP1/BI/027 strains or with hemoglobin levels lower than 10 g/dL. In the case of severe anemia, there is no obvious explanation for this finding; however, this interaction did not persist in a fully adjusted multivariate model suggesting a potential confounder. On the other hand, both subgroup analyses and multivariate analysis confirmed the smaller benefit appreciated in the few patients enrolled who were infected with NAP1/BI/027 strains treated with fidaxomicin. Of note, the data showed a nonstatistically significant 22% reduction in persistent or recurrent diarrhea or death in those with NAP1-strain infections. Given that only 292 of the 814 strains assayed were NAP1/BI/027, even in the combined dataset the number of cases was underpowered to definitively conclude whether or not fidaxomicin has a beneficial effect for treating CDI due to NAP1/BI/027 strains.

Certain groups of patients with CDI are at a significantly higher risk of recurrences including older patients, patients requiring concomitant antibiotic therapy, patients with severe renal impairment, cancer patients, and those with severe CDI (Figure 3). Post hoc subgroup analysis of combined data from studies OPT 101.1.C.003 and OPT 101.1.C.004 explored these high-risk populations. Overall, use of fidaxomicin in patients with conditions associated with a high risk for recurrence had significantly improved outcomes. In the subjects that required concomitant antibiotic therapy for concurrent infections randomized to fidaxomicin, the cure rate was 90.0% compared with 79.4% ($P = 0.04$) in those treated with vancomycin. Fidaxomicin therapy was associated with 12.3% less recurrences compared to vancomycin ($P = 0.048$). In subjects with renal impairment (RI), CDI cures declined and recurrences increased with progressively declining renal function.
Cure rates were similar for normal (91%) and mild RI (92%), but fell to 80% for moderate and 75% for severe RI ($P < 0.001$). Recurrence rates were 16%, 20%, 27%, and 24% for normal, mild, moderate, and severe RI ($P = 0.009$). Fidaxomicin was associated with significantly lower odds of recurrence (odds ratio [OR] = 0.46, confidence interval [CI] 0.32–0.66) and superior sustained response (OR = 1.85, CI 1.39–2.47) than vancomycin. In patients with severe renal dysfunction, recurrence occurred in 15% of fidaxomicin-treated subjects compared to 35% of those randomized to vancomycin. Odds of recurrence were 54% lower and odds of sustained response were 85% greater with fidaxomicin relative to vancomycin. In patients with a diagnosis of cancer, CDI cure was more likely in those randomized to fidaxomicin than in subjects on vancomycin ($P = 0.041$), recurrence was less likely ($P = 0.025$), and the sustained response rate was significantly higher ($P = 0.03$). A post hoc analysis, using regression modeling of the two pivotal double-blind randomized multicenter studies, showed that in comparison to vancomycin, those patients who were treated with fidaxomicin had a 60% lower risk of recurrence after adjusting for age, concomitant antibiotics, and $C.\ difficile$ strain.

**Advantages**

Fidaxomicin has potential advantages over other drugs used to treat CDI and a number of properties that appear to be ideally suited to the treatment of CDI. Fidaxomicin is bactericidal, with lower MICs against $C.\ difficile$ when compared to vancomycin and metronidazole, and it has a prolonged postantibiotic effect of approximately 10 hours (range 9.5–12.5 hours) allowing for twice daily dosing. After oral dosing, fidaxomicin achieves fecal concentrations well above the MIC$_{90}$ of 0.25 mcg/mL for $C.\ difficile$ with fecal concentrations within 24 hours of the last dose of 639–2710 mcg/g for fidaxomicin and 213–1210 mcg/g for OP-1118, the major metabolite of fidaxomicin. Fidaxomicin has minimal systemic absorption with plasma concentrations within the Tmax window (1–5 hours) of 0.3–197 ng/mL for fidaxomicin and 0.29–871 ng/mL for OP-1118, even in patients with severe CDI. Fidaxomicin has a very narrow spectrum of antimicrobial activity when compared to vancomycin and metronidazole; therefore, it has less impact on the normal intestinal microbiota, predominantly on the members of clostridial clusters XIVa and IV, the $Bacteroides/Prevotella$ group, and it has an indifferent effect on bifidobacteria. Clinical and bacteriological cure in patients with CDI is therefore achieved with minimal effects on the composition of the microbiome, thus allowing for a more rapid restoration of the commensal microflora, thereby reducing the risk of $C.\ difficile$ colonization, reinfection, and proliferation. Fidaxomicin has moderate activity against other gram-positive organisms, including $Staphylococcus$ sp. and $Enterococci$. In a recent study, treatment for CDI with fidaxomicin was less likely to promote acquisition of VRE and candida species when compared to vancomycin, a potential benefit in the relationship with infection control implications. Fidaxomicin blocks gene transcription,
halting bacterial sporulation and suppressing toxin production.\textsuperscript{51-53} Reappearance of toxin in fecal filtrates was observed in 28% of vancomycin-treated patients samples (29 of 94), compared with 14% of fidaxomicin-treated patient samples (13 of 91; \( P = 0.03 \)).\textsuperscript{51} In a recent study, the effects of fidaxomicin, its major metabolite (OP-1118), vancomycin, and metronidazole on the expression of toxin genes and toxin proteins in four strains of \textit{C. difficile}, including two hypervirulent NAP1/BI/027 isolates, were compared.\textsuperscript{52} Subinhibitory levels of fidaxomicin and OP-1118, but not vancomycin or metronidazole, suppressed both sporulation and toxin production (\( > 60\% \)) in \textit{C. difficile} through at least 1 week of culture.\textsuperscript{52,53} Suppression of toxin production may contribute to the improved sustained clinical response observed with fidaxomicin when compared to vancomycin.\textsuperscript{51,52} Inhibition of sporulation may well impact the rate of recurrences seen in patients treated with fidaxomicin in comparison to vancomycin and reduction of the shedding of spores has the potential benefit of decreasing transmission of \textit{C. difficile} in hospital settings; however, further studies are needed to determine this impact of fidaxomicin on \textit{C. difficile} transmission.\textsuperscript{51}

Based on online reviews, the patient satisfaction ratings are very favorable with rapid resolution of symptoms and frequency of diarrhea even after failed attempts of therapy with vancomycin and metronidazole.\textsuperscript{54-56}

### Safety and tolerability

In nonclinical studies, high doses of fidaxomicin were administered to dogs (approximately 1 g/kg/day) with no target organ toxicities reported.\textsuperscript{48} In the Phase III clinical trials, the safety profile of fidaxomicin was comparable with oral vancomycin with no differences in the rates of serious adverse events or death.\textsuperscript{22,23}

Anemia and leukopenia have been reported in patients receiving fidaxomicin and vancomycin at almost identical rates, although no specific bone marrow toxicity was observed with fidaxomicin in the nonclinical trials. In patients who developed leukopenia, the incidence of infection resulting in death was similar between fidaxomicin (2%) and vancomycin (1.9%).

Fidaxomicin is FDA category B for pregnancy as animal reproduction studies have failed to demonstrate any risk to the fetus; however, there are no adequate and well controlled studies in pregnant women.\textsuperscript{48} The available evidence is inadequate for determining infant risk when used during breastfeeding, and caution is advised when administering fidaxomicin to a nursing mother.

### Other antibiotics

#### Nitazoxanide

In small trials, nitazoxanide efficacy appears to be comparable to metronidazole and vancomycin for the treatment of CDI.\textsuperscript{57,58} Given limited studies and high cost, nitazoxanide use for the management of CDI is uncommon.

#### Rifaximin

Rifaximin is a semisynthetic, nonsystemic antibiotic with excellent in vitro activity against \textit{C. difficile} and limited impact on the intestinal microbiome. Uncontrolled small studies have evaluated rifaximin for the management of CDI unresponsive to multiple courses of metronidazole and vancomycin.\textsuperscript{59-62} Use of rifaximin in treating CDI is limited by sparse supportive evidence, acquisition cost, and due to reports of the development of \textit{C. difficile} resistance associated with its use for CDI treatment.

#### Teicoplanin

It has in vitro activity that is comparable to that of vancomycin against \textit{C. difficile}. Teicoplanin has been found to be superior to vancomycin for curing CDI; however, these clinical trial results should be interpreted with caution given that these data were derived from studies with small numbers of patients and a high risk of bias.\textsuperscript{63,64} Teicoplanin is not available for use in the United States.

#### Bacitracin

In a randomized, double blind, crossover trial, oral bacitracin demonstrated comparable effectiveness to vancomycin for the treatment of CDI.\textsuperscript{65} Bacitracin, was found to be less effective than vancomycin in eradicating \textit{C. difficile} and its toxin from patients’ stools; however, no relationship between the development of recurrences and the presence of \textit{C. difficile} and its toxins at the end of therapy could be discerned. Given in vitro evidence of resistance, bacitracin is considered to have a limited role in the therapy of CDI.\textsuperscript{64}

#### Tigecycline

Limited case reports have suggested that tigecycline alone or in combination with more traditional therapeutic options like vancomycin or metronidazole, could be used in the treatment of severe CDI when prior therapy has failed.\textsuperscript{66} The precise role of tigecycline in the treatment of CDI remains unclear and further studies are needed.

#### Fusidic acid

Fusidic acid was compared to metronidazole in the first episode of CDI. In the fusidic acid group, 83% were clinically...
cured in comparison to 93% in the metronidazole group ($P = 0.116$) at the first follow-up visit, and the rates were 27% and 29%, respectively. 67,68 The development of resistance in \textit{C. difficile} is frequent in patients treated with fusidic acid with no apparent negative impact on therapeutic efficacy noted. 67,68

**Investigational new antimicrobial and nonantimicrobial agents**

Numerous antibiotic and non-antibiotic alternatives for the treatment of CDI have been recently described or are currently under study evaluation.

**Ramoplanin**

Ramoplanin is a lipoglycodepsipeptide antibacterial with similar, but considerably more potent activity than vancomycin against \textit{C. difficile} and VRE, with little impact on anaerobic organisms and no cross resistance to vancomycin reported to date. 64,69,70 In a Phase II study, ramoplanin was compared to vancomycin for CDI treatment in 86 subjects who were randomly assigned to receive 10 days of oral therapy with either ramoplanin 200 mg twice daily ($n = 28$), ramoplanin 400 mg twice daily ($n = 29$), or vancomycin 125 mg orally four times daily ($n = 29$). 71 Clinical cure, defined as either complete or partial response, was achieved in 83% of the ramoplanin 200 mg arm, 85% in the 400 mg group, and 86% in the vancomycin group. Ramoplanin appeared to be equally effective compared to vancomycin, but larger trials are necessary to further elucidate its role in the treatment of CDI. A Phase III noninferiority protocol with vancomycin as the comparator has been approved by the FDA.

**CB-183,315**

CB-183,315 is an orally available lipopeptide antibiotic, currently in Phase III clinical development, that is structurally related to daptomycin with in vitro efficacy against VRE and \textit{C. difficile}, including strains resistant to florquinolones and metronidazole, and with elevated MICs to vancomycin. 74,75 A Phase II study compared two doses (125 mg versus 250 mg twice daily) of CB-183,315 to vancomycin (125 mg four times daily) in 209 subjects with CDI. 24 The higher dose CB-183,315 demonstrated a clinical cure rate comparable to oral vancomycin. However, while recurrence or relapse was 35.6% in the oral vancomycin arm and 27.9% in the low dose CB-183,315, in the high dose CB-183,315 group it was only 17.2% ($P = 0.035$). The NAP1/BI/027 strain of \textit{C. difficile} was isolated in 32% of subjects in this trial. The clinical response rate in these subjects was comparable across the CB-183,315 and oral vancomycin groups. A modest, but not statistically significant, reduction in relapse rates in those treated with CB-183,315 was noted.

**Non-antibiotic therapeutic alternatives**

The immune response to \textit{C. difficile} colonization is the major determinant of the magnitude and duration of clinical manifestations. Intravenous immunoglobulin (IVIg), monoclonal antibodies, immunization, and donor fecal transplantation have been used in recent years with encouraging results or are currently under study (Table 3).

| Table 3 | Non-antibiotic alternatives and investigational new agents for the management of CDI |
|--------|------------------------------------------------------------------------------------------------------|
| **Agent** | **Comments**                                                                                      |
| IVIg    | Multisystemic side effect profile. Most commonly renal failure. Efficacy for use in adults is inconclusive; in pediatrics, evidence favors efficacy. |
| Fecal transplantation | Infusion of feces from a healthy donor. Most evidence comes from single center case series and case reports. A recent multicenter, long-term follow-up study has shown positive results. |
| Probiotics | Multiple studies favor the use of probiotics for the prevention of CDI and antibiotic-associated diarrhea; however, appropriately powered studies are needed to confirm these findings. Guidelines do not recommend the routine use of probiotics given the lack of definitive evidence of effectiveness and potential risk of blood stream infection. |
| **Investigational new agents** |                                                                                                   |
| CDI and CDBI | Human monoclonal antibodies against C. difficile toxins A and B. Phase III trial for prevention of CDI, recurrence (MODIFY I [NCT01241552] and MODIFY II [NCT01513239]). 91-97 |
| ACAM-CDIFF | Active C. difficile toxoid vaccine. Phase II placebo-controlled for primary CDI prevention (NCT00772343). 93-95 |
| VP 20621 | Nontoxicogenic C. difficile. Phase II trial for prevention of CDI recurrence (NCT01259726). 96 |

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**Abbreviations:** CDI, Clostridium difficile infection; IVIg, intravenous immunoglobulin; CDI and CDBI, Clostridium difficile toxin A, C. difficile toxoid vaccine B. VP, ViroPharma.
Intravenous immunoglobulin (IVIg)/monoclonal antibodies

Although pooled IVIg has been used in cases of severe acute and recurrent CDI, there are no randomized controlled clinical trials evaluating efficacy.  

IVIg may be considered as an adjunctive treatment option in those who are hypogammaglobulinemic, have failed initial therapies, or in seriously ill patients in whom surgery is being considered, until results from large, randomized controlled trials should become available.

Human monoclonal antibodies against C. difficile toxins A (CDA1) and B (CDB1)

A single infusion of human monoclonal antibodies against C. difficile toxins A (CDA1) and B (CDB1) dosed at 10 mg/kg body weight was evaluated in a Phase II randomized, double-blind, placebo-controlled study in the treatment of 200 symptomatic individuals with CDI who were being treated with standard therapy of either metronidazole or vancomycin. The primary outcome was recurrence of infection during the 84 days after the administration of the study drug. The rate of recurrent CDI in the group of patients treated with monoclonal antibodies was 7% versus 25% in the placebo group ($P < 0.001$). The recurrence rates among patients with the epidemic BI/NAP1/027 strain were 8% for the antibody group and 32% for the placebo group ($P = 0.06$). However, there were no significant differences in the severity of diarrhea, the median or mean number of days to the resolution of diarrhea, or in treatment failures between the two groups. Phase III trials validating monoclonal antibody therapy of CDI are currently underway.

Recombinant single-domain antibody fragments targeting the cell receptor binding domain of toxin A and toxin B have shown favorable characteristics such as high production yield, potent toxin neutralization, and intrinsic stability. These recombinant single-domain antibody fragments are attractive systemic therapeutics, but more studies are needed to assess its true efficacy in the treatment of CDI.

Fecal transplantation

Fecal transplantation or bacteriotherapy, also referred to as fecal microbiota transplant and intestinal microbiota transplant, using intestinal microorganisms from a healthy donor, has been used to treat patients with relapsing CDI as an alternative to antibiotic therapy in an effort to restore normal colonic microbiota with positive results. Challenging issues including donor selection (related versus unrelated donor), screening donors for transmissible infectious diseases, standardization of stool preparation techniques, insurance reimbursement for the procedure and donor testing, and long term safety and efficacy concerns need to be evaluated systematically. A systematic literature review, including 27 studies and case reports, found 317 evaluable subjects and reported an overall success rate of 92%, with 89% of patients responding after a single treatment. Randomized controlled clinical trials are needed to support this approach and to better determine the best route of transplantation.

The first attempt at an open-label, randomized, controlled trial evaluating fecal bacteriotherapy in patients with relapsed CDI after at least one course of vancomycin or metronidazole was recently published. In this study, the subjects were randomly assigned to one of three therapeutic interventions: either vancomycin 500 mg orally four times daily for 4 or 5 days followed by bowel lavage on the last day of antibiotic therapy with subsequent infusion of donor feces through a nasoduodenal tube the next day; vancomycin 500 mg orally four times daily for 14 days; or vancomycin 500 mg orally for 4 or 5 days followed by bowel lavage on the last day of antibiotic therapy. The primary endpoint of the study was resolution of CDI-associated diarrhea (cure) without relapse at 10 weeks after initiation of the therapeutic regimen. Response rate to the fecal bacteriotherapy group was 81% after the first infusion, while in the vancomycin only group, the response rate was 31% ($P < 0.001$) and in the vancomycin followed by bowel lavage group, the response rate was 23% ($P < 0.001$). This finding supports prior uncontrolled reports and encourages further investigation into optimal use of antibiotics and fecal bacteriotherapy in the management of CDI and of the role of the fecal microbiome in the management and prevention of other gastrointestinal and metabolic conditions.

Probiotics

Probiotics are preparations of live microorganisms, including the Bifidobacterium, Saccharomyces, and Lactobacillus species, and have been used as an attempt to prevent or treat CDI. The postulated mechanisms of action advocating use of these products include the fact that probiotics enhance mucosal barrier function because they have been reported to enhance mucin secretion, provide colonization resistance, produce bacteriocins, increase production of secretory immunoglobulin A, produce a balanced T-helper cell response, as well as increase production of interleukin 10, and transform growth factor beta, both of which play a role in the development of immunologic tolerance to antigens. In vitro studies have shown that Saccharomyces boulardii acts as an antitoxin
blocking toxin receptor site and causes direct destruction of \textit{C. difficile} toxins A and B.\cite{91,92}

Recently published studies and reviews favor the use of probiotics for the prevention of CDI and antibiotic-associated diarrhea.\cite{92,93} However, many potential flaws in study designs were identified in these trials and additional, appropriately powered studies are needed to confirm these findings. Current treatment guidelines do not advocate the routine use of probiotics for the treatment of CDI given the lack of definitive evidence of effectiveness and the potential risk of bloodstream infection.\cite{1}

\textbf{ACAM-CDIFF}

A \textit{C. difficile} toxoid vaccine as an immunologic approach for the prevention and treatment of CDI is currently under investigation.\cite{94-6} An intramuscular antitoxin A and B vaccine was found to be well tolerated in 200 subjects in six Phase I studies with successful subsequent production of IgG against toxin A and B in most subjects.\cite{94,95} Lower response rates in those aged over 70 years compared with those aged 25 years were observed. A Phase II study was completed in June 2012 comparing \textit{C. difficile} toxoid vaccine versus toxoid vaccine with adjuvant versus placebo. The final results of this study have not been published.\cite{96}

\textbf{Clostridium difficile-conjugated vaccines}

\textit{C. difficile} can express three polysaccharides (PS-1, PS-2, and PS-3) on the surface of the microorganism.\cite{97-99} Current ongoing investigations using PS-2, a complex made up of hexaglocosyl repeating blocks as targets for conjugated \textit{C. difficile} vaccines, are in development. A glucoconjugate vaccine composed of PS-2 and the diphtheria toxoid variant CRM has been shown to be highly immunogenic in mice.\cite{97} Two independent studies have described the chemical synthesis of the phosphorylated and nonphosphorylated hexaglycosyl repeating blocks of PS-2.\cite{98,99} These molecules, when conjugated to a protein carrier, are immunogenic in mice. Notably, these investigators have described that the stools of hospitalized patients infected with \textit{C. difficile} were found to contain specific IgA antibodies that recognize the synthetic nonphosphorylated hexasaccharide, suggesting that PS-2 is antigenic in humans.\cite{99} Both the natural polysaccharide and the synthetic substructure are currently under study as potential conjugate vaccine candidates against CDI.

\textbf{VP 20621}

VP20621 is comprised of non-toxigenic \textit{C. difficile} spores that have been shown to be protective against CDI challenge in the hamster model.\cite{100} In humans, multiple doses of VP20621 were well tolerated in 27 volunteers at all dose levels, and oral administration resulted in positive non-toxigenic \textit{C. difficile} stool cultures by day 6, suggesting rapid colonization of the GI tract. Currently, a Phase II trial, evaluating the safety and efficacy of VP20621 administered after the completion of standard CDI therapy for the prevention of recurrence of CDI in adults is ongoing.\cite{39,101}

\textbf{Conclusion}

Fidaxomicin represents an important development in the treatment of CDI with significant advantages over the other currently available antimicrobial agents. Fidaxomicin should be considered as first-line therapy for the management of CDI with high risk for relapse and recurrent CDI especially in those populations, including those receiving concomitant antibiotics, those with first relapse of CDI, those with renal dysfunction, older individuals, and in those with cancer.\cite{12,37,41}

\textbf{Disclosure}

Fredy Chaparro-Rojas has no conflicts of interest to report. Kathleen M Mullane is on advisory boards for Optimer Pharmaceuticals and Merck and is involved in clinical trials for Actelion Pharmaceuticals, Astellas Pharma, Chimerix, Merck, Optimer Pharmaceuticals, and ViroPharma. The authors report no other conflicts of interest in this work.

\textbf{References}

1. Cohen SH, Gerding DN, Johnson S, et al; for Society for Healthcare Epidemiology of America, Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). \textit{Infect Control Hosp Epidemiol}. 2010;31(5):431–455.

2. Bartlett JG, Taylor NS, Chang T, Dzink J. Clinical and laboratory observations in Clostridium difficile colitis. \textit{Am J Clin Nutr}. 1980;33(Suppl 11):2521–2526.

3. George WL, Rolfe RD, Finegold SM. Clostridium difficile and its cytotoxin in feces of patients with antimicrobial agent-associated diarrhea and miscellaneous conditions. \textit{J Clin Microbiol}. 1982;15(6):1049–1053.

4. Kelly CP, Pothoulakis C, LaMont JT. Clostridium difficile colitis. \textit{N Engl J Med}. 1994;330(4):257–262.

5. Lucado J, Gould C, Elixhauser A. Clostridium Difficile Infections (CDI) in Hospital Stays, 2009. Healthcare Cost and Utilization Project Statistical Brief #124. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available from: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf. Accessed April 29, 2013.

6. Raffi F, Sutherland JB, Cerniglia CE. Effects of treatment with antimicrobial agents on the human colonic microflora. \textit{Ther Clin Risk Manag}. 2008;4(6):1343–1358.

7. Sun X, Savidge T, Feng H. The enterotoxicity of \textit{Clostridium difficile}. \textit{Toxins (Basel)}. 2010;2(7):1848–1880.

8. Starr JM, Impallomeni M. Risk of diarrhoea, \textit{Clostridium difficile} and cefotaxime in the elderly. \textit{Biomed Pharmacother}. 1997;51(2):63–67.
9. Barc MC, Depitre C, Cortheir G, Collignon A, Su WJ, Bourlioux P. Effects of antibiotics and other drugs on toxin production in Clostridium difficile in vitro and in vivo. *Antimicrob Agents Chemother*. 1992;36(6):1332–1335.

10. Lessa FC, Gould CV, McDonald LC. Current status of Clostridium difficile infection epidemiology. *Clin Infect Dis*. 2012;55 Suppl 2:S65–S70.

11. Bartlett JG. The case for vancomycin as the preferred drug for treatment of Clostridium difficile infection. *Clin Infect Dis*. 2008;46(10):1489–1492.

12. Mullane KM, Miller MA, Weiss K, et al. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. *Clin Infect Dis*. 2011;53(5):440–447.

13. Bauer MP, Kuiper EJ, van Dissel JT; for European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). *Clin Microbiol Infect*. 2009;15(12):1067–1079.

14. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *Am J Infect Control*. 1995;23(2):87–94.

15. Al-Nassir WN, Sethi AK, Li Y, Pultz MJ, Biggs MM, Donnelly CJ. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of Clostridium difficile-associated disease. *Antimicrob Agents Chemother*. 2008;52(7):2403–2406.

16. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302–307.

17. Louie TJGM, Grimard D, Johnson S, Poirier A, Weiss K; for the Tolevaler Study Group. Results of a phase III trial comparing tolevaler, vancomycin and metronidazole in patients with Clostridium difficile-associated diarrhea [abstract K-425a]. 2007.

18. Aslam S, Hamill RJ, Mushier DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. *Lancet Infect Dis*. 2005;5(9):549–557.

19. Baines SD, O’Connor R, Freeman J, et al. Emergence of reduced susceptibility to metronidazole in Clostridium difficile. *J Antimicrob Chemother*. 2008;62(5):1046–1052.

20. Rupnik M, Wilcox MH, Gerdon DN. Clostridium difficile infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol*. 2009;7(7):526–536.

21. Bolton RP, Culshaw MA. Facial metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to Clostridium difficile. *Gut*. 1986;27(10):1169–1172.

22. Louie TJ, Miller MA, Mullane KM, et al; for OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med*. 2011;364(5):422–431.

23. Cornely OA, Crook DW, Esposito R, et al; for OPT-80-004 Clinical Study Group. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281–289.

24. Patino HSC, Louie T, Bernardo P, Friedland I; for the CDI Study Group. Efficacy and safety of the lipopeptide CB-183,315 for the treatment of Clostridium difficile infection [Abstract K-205a]. Proceedings of the 51st Internatnl Congr Antimicr Ag Chemother; September 17–20, 2011; Chicago, IL.

25. Johnson S. Recurrent Clostridium difficile infection: a review of risk factors, treatments, and outcomes. *J Infect*. 2009;58(6):403–410.

26. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol*. 2002;97(7):1769–1775.

27. Mullane KM, Gorbach S. Fidaxomicin: first-in-class macrolide antibiotic. *Expert Rev Anti Infect Ther*. 2011;9(7):767–777.

28. Parenti F, Pagani H, Beretta G. Lipiarmycin, a new antibiotic from Actinoplanes. I. Description of the producer strain and fermentation studies. *J Antimicrob Agents Chemother*. 1995;28(4):247–252.

29. Theriault RJ, Karwowski JP, Jackson M, et al. Tiacumicins, a novel complex of 18-membered macrolide antibiotics. I. Taxonomy, fermentation and antibacterial activity. *J Antimicrob Agents Chemother*. 1995;40(5):567–574.

30. Goldstein EJ, Citron DM, Sears P, Bahakhani F, Sambol SP, Gerding DN. Comparative susceptibilities to fidaxomicin (OPT-80) of isolates collected at baseline, recurrence, and failure from patients in two phase II trials of fidaxomicin against Clostridium difficile infection. *Antimicrob Agents Chemother*. 2011;55(11):5194–5199.

31. Biedenbach DJ, Ross JE, Putnam SD, Jones RN. In vitro activity of fidaxomicin (OPT-80) tested against contemporary clinical isolates of Staphylococcus spp. and Enterococcus spp. *Antimicrob Agents Chemother*. 2010;54(5):2273–2275.

32. Bronfman E, White RJ, Lancini GC, Parenti F. Lipiarmycin, a new antibiotic from Actinoplanes. II. Isolation, chemical, biological and biochemical characterization. *J Antimicrob Agents Chemother*. 1975;28(4):253–259.

33. Seddon JSP. Preliminary OPT-80 Mode of Action Studies. *Optimer Pharmaceuticals, Inc. Report Number BIO0902034. 2003.

34. Sergio S, Pirali G, White R, Parenti F. Lipiarmycin, a new antibiotic from Actinoplanes III. Mechanism of action. *J Antimicrob Agents Chemother*. 1975:28(7):543–549.

35. Srivastava A, Talaue M, Liu S, et al. New target for inhibition of bacterial RNA polymerase: ‘switch region’. *Curr Opin Microbiol*. 2011;14(5):532–543.

36. Sears PBF, Citron DM. Typing and Susceptibility of Bacterial Isolates from the OPT-80 (PAR-101) Phase 2A Study for C. difficile-associated Diarrhea. [Poster] 9th Biennial Congress of the Anaerobe Society of the Americas, Long Beach, CA; 2008.

37. Crook DW, Walker AS, Kean Y, et al; for Study 003/004 Teams. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. *Clin Infect Dis*. 2012;55 Suppl 2:S593–S603.

38. Mullane KGY, Crook D, Cornely OA, Miller M, Louie T, Gorbach S. Renal Impairment and Response to Fidaxomicin versus Vancomycin in Patients with Clostridium difficile Infection [abstract]. Proceedings of the 49th Annual Infectious Diseases Society of America Meeting. October 20–23, 2011; Boston MA.

39. Cornely OAMM, Fantin B, Mullane K, Kean Y, Gorbach S. Clostridium difficile-associated diarrhea in cancer patients treated with fidaxomicin or vancomycin. Proceedings of the American Society of Clinical Oncology Abstract #9067; June 1–5, 2012; Chicago, IL.

40. Cornely OAMM, Fantin B, Mullane K, Kean Y, Gorbach S. Clinical outcomes for cancer patients with Clostridium difficile infection (CDI) Poster 2289. Proceedings of the European Congress of Clinical Microbiology and Infectious Diseases. March 31–April 3, 2012; London, UK.

41. Louie TJ, Miller MA, Crook DW, et al. Effect of age on treatment outcomes in Clostridium difficile infection. *J Am Geriatr Soc*. 2013;61(2):222–230.

42. Johnson AP. Drug evaluation: OPT-80, a narrow-spectrum macrocyclic antibiotic. *Curr Opin Investig Drugs*. 2007;8(2):168–173.

43. Babakhani F, Gomez A, Robert N, Sears P. Postantibiotic effect of fidaxomicin and its major metabolite, OP-1118, against Clostridium difficile. *Antimicrob Agents Chemother*. 2011;55(9):4427–4429.

44. Sears P, Louie T, Mullane KM, et al. Pharmacokinetics/pharmacodynamics (PK/PD) of fidaxomicin in treatment of Clostridium difficile infection (CDI). Proceedings of the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). September 12–15, 2010; San Francisco, CA.

45. Louie T, Miller M, Donskey C, Mullane K, Goldstein EJ. Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with Clostridium difficile infection. *Antimicrob Agents Chemother*. 2009;53(1):223–228.
46. Okumu FWR, Sears R, Shue YK. Safety and Pharmacokinetics of OPT-80, a novel antibiotic for treatment of Clostridium difficile-associated diarrhea (CDAD). Proceedings of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). October 30–November 2, 2004; Washington, DC.

47. Sears P, Crook DW, Louie TJ, Miller MA, Weiss K. Fidaxomicin attains high fecal concentrations with minimal plasma concentrations following oral administration in patients with Clostridium difficile infection. Clin Infect Dis. 2012;55 Suppl 2:S116–S120.

48. DIFICID® [prescribing information]. San Diego, CA: Optimer Pharmaceuticals, Inc; May 2011. Data on File. Clinical Study Report OPT-8004 Final. June 4, 2010. Optimer Pharmaceuticals, Inc, Data on File. Clinical Study Report OPT-8003 Final. June 17, 2010 (Version 2). Optimer Pharmaceuticals, Inc. Available from: http://www.drugs.com/comments/fidaxomicin/dificid.html. Accessed April 29, 2013.

49. Tannock GW, Munro K, Taylor C, et al. A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of Clostridium difficile-infected patients than does vancomycin. Microbiology. 2010;156(Pt 1):3354–3359.

50. Nerandzic MM, Mullen K, Miller MA, Babakhani F, Donskey CJ. Reduced acquisition and overgrowth of vancomycin-resistant enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. Clin Infect Dis. 2012;55 Suppl 2:S121–S126.

51. Louie TJ, Cannon K, Byrne B, et al. Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. Clin Infect Dis. 2012;55 Suppl 2:S132–S142.

52. Babakhani F, Bouillault L, Sears P, Sims C, Gomez A, Sonenstein AL. Fidaxomicin inhibits toxin production in Clostridium difficile. J Antimicrob Chemother. 2013;68(3):515–522.

53. Babakhani F, Bouillault L, Gomez A, Sears P, Nguyen L, Sonenstein AL. Fidaxomicin inhibits spore production in Clostridium difficile. Clin Infect Dis. 2012;55 Suppl 2:S162–S169.

54. DIFICID™ oral tablets, fidaxomicin oral tablets [prescribing information]. San Diego, CA: Optimer Pharmaceuticals, Inc; 2011.

55. Miller MAMK, Weiss K, Lentnek A, et al. Faster time to resolution of diarrhea with fidaxomicin vs vancomycin in patients with Clostridium difficile infection: a phase 2 study [abstract K-985a]. Proceedings of the 44th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy. October 30–November 2, 2004; Washington, DC.

56. Cornely OA. Current and emerging management options for Clostridium difficile infection: what is the role of fidaxomicin? Clin Microbiol Infect. 2012;18 Suppl 6:28–35.

57. Venugopal AA, Johnson S. Current state of Clostridium difficile treatment options. Clin Infect Dis. 2012;55 Suppl 2:S71–S76.

58. Snyderman DR, Jacobus NV, McDermott LA. Activity of a novel cyclic lipopeptide, CB-183,315, against resistant Clostridium difficile and other Gram-positive aerobic and anaerobic intestinal pathogens. Antimicrob Agents Chemother. 2012;56(6):3448–3452.

59. Mascio CT, Mirtin L, Howland KT, et al. In vitro and in vivo characterization of CB-183,315, a novel lipopeptide antibiotic for treatment of Clostridium difficile. Antimicrob Agents Chemother. 2012;56(10):5023–5030.

60. Saiio T, Kimura S, Tateda K, et al. Evidence of intravenous immuno-globulin as a critical supportive therapy against Clostridium difficile toxin-mediated lethality in mice. J Antimicrob Chemother. 2011;66(5):1096–1099.

61. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrrhea. J Antimicrob Chemother. 2004;53(5):882–884.

62. Juang P, Skledar SJ, Zghieb NK, et al. Clinical outcomes of intravenous immune globulin in severe clostridium difficile-associated diarrhea. Am J Infect Control. 2007;35(2):131–137.

63. Leung DV, Kelly CP, Boguniewicz M, Pothoulakis C, LaMont JT, Flores A. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. J Pediatr. 1991;118(4 Pt 1):633–637.

64. Abougergi MS, Kwon JH. Intravenous immunoglobulin for the treatment of recurrent Clostridium difficile infection: a review. Dig Dis Sci. 2011;56(1):19–26.

65. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. New Engl J Med. 2010;362(3):197–205.

66. ClinicalTrials.gov. A study of MK-3415, MK-6072, and MK-3415A in participants receiving antibiotic therapy for Clostridium difficile infection (MK-3415A-001 AM2) (MODIFY I). ClinicalTrials.gov; 2013. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01241552. Accessed April 29, 2013.
83. ClinicalTrials.gov. A study of MK-6072 and MK-3415A in participants receiving antibiotic therapy for Clostridium difficile infection (MK-3415A-002) (MODIFY II). ClinicalTrials.gov; 2013. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01513239. Accessed April 29, 2013.
84. Hussack G, Arbabi-Ghahroudi M, van Faassen H, et al. Neutralization of Clostridium difficile toxin A with single-domain antibodies targeting the cell receptor binding domain. J Biol Chem. 2011;286(11): 8961–8976.
85. Borody TJ, Warren EF, Leis SM, Surace R, Ashman O, Siarakas S. Bacteriotherapy using fecal flora: taming with human motions. J Clin Gastroenterol. 2004;38(6):475–483.
86. Khanna S, Pardi DS. Clostridium difficile infection: new insights into management. Mayo Clin Proc. 2012;87(11):1106–1117.
87. Bakken JS, Borody T, Brandt LJ, et al; for Fecal Microbiota Transplantation Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2011;9(12): 1044–1049.
88. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011;53(10):994–1002.
89. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. 2013;368(5): 407–415.
90. Videlock EJ, Cremonini F. Meta-analysis: probiotics in antibiotic-associated diarrhea. Aliment Pharmacol Ther. 2012;35(12): 1355–1369.
91. Friedman G. The role of probiotics in the prevention and treatment of antibiotic-associated diarrhea and Clostridium difficile colitis. Gastroenterol Clin North Am. 2012;41(4):763–779.
92. Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med. 2012;157(12):878–888.
93. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA. 2012;307(18):1959–1969.
94. Foglia G, Shah S, Luxenburger C, Pietrobon PJ. Clostridium difficile: development of a novel candidate vaccine. Vaccine. 2012;30(29):4307–4309.
95. Folgia G. ACAM-CDIFF: An active vaccine against Clostridium difficile infection. Proceedings of the 10th Anaerobe Society of the Americas. July 7–10, 2010.
96. ClinicalTrials.gov. Study of a Clostridium difficile toxoid vaccine (ACAM-CDIFFTM) in subjects with Clostridium difficile infection [webpage on the Internet]. ClinicalTrials.gov; 2012. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00772343. Accessed April 29, 2013.
97. Cappelletti E, Romano MR, Cakici OS, et al. Conjugate vaccine against Clostridium difficile. Glycoconjunct J. 2011;28:265.
98. Danielli E, Lay L, Proietti D, Berti F, Costantino P, Adamo R. First synthesis of C. difficile PS-II cell wall polysaccharide repeating unit. Org Lett. 2011;13(3):378–381.
99. Oberli MA, Hecht ML, Bindschädler P, Adibekian A, Adam T, Seeberger PH. A possible oligosaccharide-conjugate vaccine candidate for Clostridium difficile is antigenic and immunogenic. Chem Biol. 2011;18(5):580–588.
100. Merrigan MM, Sambol SP, Johnson S, Gerding DN. New approach to the management of Clostridium difficile infection: colonisation with non-toxigenic C. difficile during daily ampicillin or ceftriaxone administration. Int J Antimicrob Agents. 2009;33 Suppl 1:546–550.
101. ClinicalTrials.gov. Safety and efficacy of VP20621 for prevention of recurrent Clostridium difficile infection [webpage on the Internet]. ClinicalTrials.gov; 2012. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01259726. Accessed April 29, 2013.
102. Cornely OA, Miller MA, Louie TJ, et al. Treatment of first recurrence of Clostridium difficile infection [webpage on the Internet]. ClinicalTrials.gov; 2013. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01513239. Accessed April 29, 2013.