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Emerging Therapies for *Clostridium Difficile* Infection

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Abstract

Objective: To review the current literature on emerging antibiotic and non-antibiotic therapies for treatment and prevention of recurrence of *Clostridium Difficile* Infection (CDI).

Data Sources: A literature search was performed using PubMed (1975 to November 2017), International Pharmaceutical Abstracts (1970 to November 2017), and MEDLINE (1946 to November 2017) to identify studies for inclusion. The following search terms were used: *Clostridium difficile, C. difficile* infection*, ridinilazole, cadazolid, bezlotoxumab, fecal microbiota transplantation*.

Study Selection and Data Extraction: All English-language phase II to III studies evaluating efficacy and/or safety of *ridinilazole, cadazolid, bezlotoxumab*, and *Fecal Microbiota Transplantation* (FMT) were included.

Data Synthesis: Phase II clinical data demonstrates that ridinilazole and cadazolid provide an improved sustained clinical response rate compared to vancomycin. The currently approved monoclonal antibody, bezlotoxumab, has demonstrated protection against recurrent CDI when used in combination with oral standard-of-care antibiotics. FMT may be a potential option for patients with recurrent CDI; however, the data is limited to relatively small, open-label trials in patients with multiple recurrences of CDI. Newer therapies currently in clinical trials have shown to be effective in treating and preventing recurrence of CDI.

Conclusion: There are a number of promising agents currently in development that could provide new options for treatment and prevention of recurrent CDI.

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Introduction

Clostridium difficile, a Gram-positive, anaerobic, spore-forming bacteria, is the most frequent cause of infectious diarrhea in hospitals and other health care settings[1-3]. Prior antibiotic use can cause disturbance of normal gut microbiota allowing for overgrowth and colonization of toxigenic strains of *C. difficile* in the colon. The presence of clostridial toxins A and B triggers an inflammatory response which causes damage to intestinal mucosa causing symptoms ranging from mild diarrhea to fatal pseudomembranous colitis, colonic rupture, and death[2,4].

Current pharmacologic options for *C. Difficile* Infection (CDI) include metronidazole, oral vancomycin, and fidaxomicin. A particular concern with the current management of CDI is disease recurrence in 20 - 30% of patients even after successful treatment[3]. Patients who have experienced at least one recurrence of CDI are at significantly increased risk of additional recurrences[5]. Further disruption of the gut microbiota is a potential limitation of oral vancomycin and metronidazole use. Additionally, recent studies have demonstrated a reduction in susceptibility to antibiotics used for CDI treatment, particularly metronidazole[6-8]. Thus, ideal treatment of CDI would target *C. difficile* specifically whilst minimizing the disruption of gut microbiota and preventing the spread of resistance.

Several novel antibiotic and non-antibiotic therapies are being developed that demonstrate activity against *C. difficile* while sparing the intestinal microbiota. This article will review the new antibiotic and non-antibiotic therapies, ridinilazole, cadazolid, bezlotoxumab and FMT, in clinical development for treatment and/or prevention of recurrence of CDI.

Methods

A systematic search was performed using PubMed (1975 to November 2017), International Pharmaceutical Abstracts (1970 to November 2017), and MEDLINE (1946 to November 2017). Combinations of the following search terms were used: *Clostridium difficile, C. difficile infection, ridinilazole, cadazolid, bezlotoxumab, fecal microbiota transplantation*. References from retrieved articles were manually searched for additional citations. Clinicaltrials.gov was searched for ongoing research. All English-language phase II to III studies assessing the efficacy and/or safety were evaluated. Only Randomized Controlled Trials (RCTs) were included. All studies included are summarized in Table 1.

Table 1: Summary of Evidence for Therapies for treatment and/or prevention of recurrence of *Clostridium difficile* infection.

Clinical Trials	Patient Characteristics	Treatment	Comparator	Harms
Ridinilazole				
Vickers et al.[16] **N = 100**	Phase II MC, DB, RCT 87% no history of rCDI 80% non-severe CDI	Oral ridinilazole 200 mg BID for 10 days N = 50	Oral vancomycin 125 mg QID or 10 days N =5 0	Rates of AEs and SAEs similar among both treatment groups
		SCR: 66.7% rCDI: 14.3% Clinical cure rate: 77.8%	SCR: 42.4% rCDI: 34.8% Clinical cure rate: 69.7%	
		SCR improvement of 21.1% (90%CI 3.1% to 39.1%) Clinical cure rate NI margin was 15% (90%CI -9.3% to 25.8%)		
Cadazolid				
Louie et al.[21] **N = 84**	Phase II, dose-finding MC, BD, RCT 79.5% first occurrence 91% Non-severe CDI	Oral cadazolid (250, 500, or 1000 mg) BID for 10 days N = 62	Oral vancomycin 125 mg QID for 10 days N = 22	Patients with at least one TEAE: Cadazolid: 22.7 – 30% Vancomycin: 45.5%
		Clinical Cure rate: 68.4%-76.5% rCDI: 18.2% to 25%	Clinical Cure rate: 68.2% rCDI: 50%	
		SCR: 46.7% to 60%	SCR: 33.3%	
		Authors concluded cadazolid was as well tolerated and efficacious as oral vancomycin.		
		Clinical cure rate: 79%	Clinical cure rate: 83.6%	
		Clinical cure rate difference 4.6%, (95% CI -11.0 to 1.9)		
Bezlotoxumab				
Lowy et al.[24] **N = 200**	Phase II Metronidazole 70-78% vancomycin + stool test for CD toxin in previous 14 days	ACT+BEZ 10 mg/kg single infusion N = 101	Placebo N=99	SAEs: Similar between groups
		rCDI: 7%	rCDI: 25%	
		P < 0.001		
		Time to recurrence RR 0.23; p = 0.01		
		rCDI among patients with > 1 previous CDI: 7%	rCDI among patients with > 1 previous CDI: 38%	
		P = 0.006		
Wilcox et al.[25] **N = 2655**	Phase III PC, DB, RCT In addition to oral standard of care antibiotics (46.7% metronidazole, 47.7% vancomycin, and 3.6% fidaxomicin)	ACT+BEZ 10 mg/kg single infusion N = 777	ACT 10 mg/kg single infusion N = 236 (this arm was stopped early due to reduced efficacy)	BEZ10 mg/kg single infusion N = 786	Placebo N = 781	Overall AEs similar among groups, except higher in the ACT group. SAEs and deaths higher with ACT.
		rCDI: 15%	rCDI: ---	rCDI: 17%	rCDI: 27%	
		rCDI differences between each group, p < 0.001				
		SCR: 58% p = 0.09 vs. placebo		SCR: 64% P = 0.0001 vs. placebo	SCR: 54%	

Fecal Microbiota Transplantation					
Van Nood et al.[31] **N = 43**	SC, OL, RCT Aged ≥18 years History of rCDI (range: 1-9)	FMT via nasoduodenal tube (unrelated donor) N = 16	Oral vancomycin 500 mg QID for 14 days N = 13	Oral vancomycin 500 mg QID for 14 days plus bowel lavage at day 4 or 5 N = 13	Overall AEs and SEAs similar among groups
		Clinical cure: 94% with 81% achieving clinical cure following single infusion	Clinical cure: 31%	Clinical cure: 23%	
Cammarota et al.[32] **N = 39**	SC, OL, RCT Aged ≥ 18 years History of rCDI (median recurrence: 3)	FMT via colonoscopy (unrelated donor) N = 20	Oral vancomycin 125 mg QID for 14 days plus bowel lavage at day 1 or 2 N = 19		Death related to CDI complications: FMT: 2 Vancomycin: 2
		Clinical cure: 90% with 65% achieving clinical cure following single infusion	Clinical cure: 26%		Overall AEs similar among groups
		P < 0.0001			
Kelly et al.[33] **N = 46**	MC, DC, RCT Age 18-74 years History of ≥ 3 rCDIs	Heterologous FMT via colonoscopy (unrelated donor) N = 22	Autologous FMT via colonoscopy N = 24		Overall AEs similar among groups
		Clinical cure in mITT: 90.9%	Clinical cure in mITT: 62.5%		
		P = 0.042			
		Overall clinical cure rate 94% (29/31 patients)	Retreatment with heterologous FMT: clinical cure (90%)		
Youngster et al.[34] **N = 20**	SC, OL, RCT Age 7-90 History of rCDI	FMT via colonoscopy (unrelated donor) N = 10	FMT via NGT (unrelated donor) N = 10		Overall AEs similar among groups
		Clinical cure: 80% following single infusion	Clinical cure: 60% following single infusion		
		Single infusion cure rate: 70% Overall cure rate: 90%¶			
Lee et al.[35] **N = 232**	MC, DL, RCT Aged ≥ 18 years History of rCDI; 84-93% < 2 rCDI	Frozen-then-thawed FMT via enema (unrelated donor) N = 118	Fresh FMT vi enema (unrelated donor) N = 114		Overall AEs similar among groups
		Clinical resolution in per-protocol population: 76/91 (83.5%)	Clinical resolution in per-protocol population: 74/87 (85.1%)		
		Difference -1.6% (95% 1-sided CI -10.5% to ∞, p = 0.01 for non inferiority)			

AC, active control; ACT, actoxumab; AE, adverse event; BEZ, bezlotoxumab; BID, twice daily; CD, *Clostridium difficile*; CDI, *Clostridium difficile* infection; CI, confidence interval; DB, double blind; FMT, fecal microbiota transplantation; MC, multiple center; mITT, modified intention-to-treat; NGT. Nasogastric tube; NI, non-inferior; NR, not reported; OL, open label; PC, placebo control; QID, four times daily; rCDI, recurrent *Clostridium difficile* infection; RCT, randomized control trial; SAE, severe adverse event; SC, single center; SCR, sustained clinical
¶ Five of the 6 patients take did not achieve cure following single infusion were given additional infusion of FMT via NGT

Ridinilazole

Ridinilazole is a novel antimicrobial agent with a narrow spectrum of activity that is currently in clinical development for the treatment of CDI. Ridinilazole displays targeted activity against *C. difficile* with little or no activity against gram-negative and most gram-positive aerobes and anaerobes and has demonstrated efficacy in both *in vitro* gut and *in vivo* hamster models[9-13]. The mechanism of action of ridinilazole is not fully understood; however, fluorescent-labeling studies indicate that ridinilazole may impair cell division and lead to an absence of septum formation[14]. Pre-clinical data indicate that ridinilazole causes minimal damage to the gut microbiota[15].

Evaluation of Clinical Efficacy and Safety

The CoDIFy trial was a multi-center, double-blind, RCT that assessed the efficacy and safety of ridinilazole compared with oral vancomycin in patients with CDI. A total of 100 patients were randomized to receive either ridinilazole 200 mg twice daily (BID) or oral vancomycin 125 mg four times daily (QID) for 10 days. The majority (87%) of patients enrolled had no history of recurrent CDI with 80% of CDIs considered non-severe.

In the modified intent-to-treat population (n = 69), ridinilazole demonstrated superiority on sustained clinical response rates (absence of recurrent disease for the next 30 days) compared to vancomycin (24 [66.7] vs. 14 [42.4%]; difference

21.1%; 90% CI 3.1-39.1%; p = 0.0004). The improvement in sustained clinical response rate was driven by reduction in rate of recurrent CDI in ridinilazole treated patients (14.3%) compared to vancomycin treated patients (34.8%). The rates of clinical cure were 77.8% and 69.7% for ridinilazole and vancomycin (90% CI -9.3% - 25.8%), respectively, meeting the non-inferiority. The incidence of treatment-emergent adverse events and serious adverse effects was similar between treatments[16].

Currently, one phase II clinical trial (NCT02784002) comparing the efficacy and safety of ridinilazole versus fidaxomicin for treatment of CDI that has completed. In September 2017, Summit Therapeutics, the developer of ridinilazole, was awarded a contract from the US government's Biomedical Advanced Research and Development Authority for continued research. The company is currently planning to initiate phase III trials in the beginning of 2018[17].

Cadazolid

Cadazolid is a novel oxazolidinone-type antibiotic currently in clinical development for the treatment of CDI. It has shown potent in vitro activity against *C. difficile* clinical isolates while having a minimal impact on normal gut microbiota[18]. The spectrum of cadazolid is largely limited to Gram-positive bacteria, with little to no activity against Gram-negative bacteria[19]. Cadazolid acts primarily on protein synthesis as a translation inhibitor with weak inhibition of DNA synthesis as a secondary effect[20].

Evaluation of Clinical Efficacy and Safety

One double-blind, phase II study has been published detailing the efficacy and safety of cadazolid in adult patients with CDI, with a first occurrence or first recurrence[21] randomized 84 subjects to either 250, 500, or 1000 mg oral cadazolid BID or 125 mg oral vancomycin QID for 10 days. CDI was considered non-severe in the majority of patients (91%) enrolled in the study; additionally, the majority of patients presented with first occurrence of CDI (79.5%) and without prior treatment with metronidazole or vancomycin (70.5%).

The results showed that the proportion of patients achieving clinical cure was similar among all cadazolid groups compared to the vancomycin group (250 mg: 76.5% (p = 0.57), 500 mg: 80% (p = 0.41), and 1000 mg: 68.4% (p = 0.83) vs. 68.2% for vancomycin). However, recurrence rates were numerically lower for all doses of cadazolid (18.2%, 25%, and 22.2%, respectively) compared to vancomycin (50.0%). Additionally, the percent of patients achieving a sustained clinical response was numerically higher with all doses of cadazolid (60%, 56.3%, and 46.7%, respectively) compared to vancomycin (33.3%). P values and confidence intervals were not reported. Across all treatment groups, no serious adverse events were related to study treatment[21].

Currently, two phase III RCTs, NCT01987895 and NCT01983683, which are part of the International Multi-center Program Assessing Cadazolid Treatment in patients suffering from *Clostridium difficile*-associated diarrhea (IMPACT) program comparing the efficacy and safety of cadazolid versus vancomycin for treatment of CDI, have completed. Preliminary analysis showed that IMPACT 1 met its primary endpoint, while IMPACT 2 failed to meet the primary endpoint. Although, cadazolid did demonstrated acceptable tolerability and safety. However, full analysis of study results has yet to be completed[22].

Bezlotoxumab

Bezlotoxumab is a human monoclonal antibody against *C. difficile* toxin B indicated to reduce the recurrence of CDI in patients receiving standard of care antibiotic treatment for CDI. In October 2016, the United States Food and Drug Administration approved bezlotoxumab for use in adults (≥ 18 years of age) receiving antibacterial drug treatment for CDI and are at high risk for recurrent CDI. Bezlotoxumab acts by direct neutralization of *C. difficile* toxin B and prevention of toxin-induced epithelial damage and subsequent inflammatory response without affecting toxin A[23].

Evaluation of Clinical Efficacy and Safety

Lowy, *et al*[24]. Conducted a phase II trial comparing the efficacy of the addition of bezlotoxumab plus actoxumab to metronidazole or vancomycin in preventing the recurrence of CDI. A total of 200 patients with a positive stool test for a *C. difficile* toxin were randomized to receive a single infusion of bezlotoxumab plus actoxumab 10 mg/kg or placebo in addition to standard antibiotic treatment (metronidazole or vancomycin). The majority of patients (70 - 78%) in both treatment arms received metronidazole[24].

The rate of laboratory-documented recurrence of CDI was significantly lower in the bezlotoxumab plus actoxumab group compared to the placebo group (7 vs. 25%, p < 0.001). Time to recurrence of *C. difficile* infection was significantly longer (p < 0.001) and the relative risk (RR) of recurrence significantly lower (RR 0.23; p = 0.01) in the bezlotoxumab plus actoxumab group compared with the placebo group. The recurrence rates among patients with more than one previous episode of CDI were significantly lower for the bezlotoxumab plus actoxumab group compared to the placebo group (7 vs. 38%, p = 0.006). There was a trend towards a lower proportion of patients in the bezlotoxumab plus actoxumab group (18%; 18/101) reporting at least one serious adverse event compared with the placebo group (28%; 28/99; p = 0.09)[24].

The efficacy of a single 10 mg/kg intravenous infusion of bezlotoxumab in patients receiving standard antibiotic treatment (metronidazole, vancomycin, or fidaxomicin) for primary or recurrent CDI was evaluated in two 12-week, phase III, double-blind trials (MODIFY I and MODIFY II)[25]. A total of 2655 patients were randomized to receive a single infusion of actoxumab plus bezlotoxumab 10 mg/kg, actoxumab 10 mg/kg, bezlotoxumab 10 mg/kg, or placebo in addition to oral standard-of care antibiotics. The actoxumab alone treatment arm was only included in the MODIFY I trial and was stopped after an interim analysis due to efficacy and safety concerns.

In MODIFY I and MODIFY II, rate of recurrent CDI was significantly lower in the bezlotoxumab alone treatment group compared to placebo (MODIFY I: 17% vs. 28%; difference, -10.1; 95% CI, -15.9 to -4.3; MODIFY II: 16% vs. 28%; difference, -9.9; 95% CI, -15.5 to -4.3; both p < 0.001) and significantly lower in the bezlotoxumab plus actoxumab treatment group compared to placebo (MODIFY I: 16% vs. 28%; difference, -11.6; 95% CI, -17.4 to -5.9; MODIFY II: 15% vs. 28%; difference, -10.7; 95% CI, -16.4 to -5.1; both p < 0.001). There was no significant difference in the rate of recurrent infection

between bezlotoxumab and actoxumab-bezlotoxumab in both trials. Additionally, there was no difference in rate of recurrence based on the choice of standard of care antibiotics. However, the majority of patients (94.4%) received either vancomycin (46.7%) or metronidazole (47.7%). Across patients at high risk for recurrent CDI, a pooled analysis found that treatment with bezlotoxumab alone or in combination with actoxumab resulted in significantly lower rates of recurrent infection compared to vancomycin alone (15 and 17 vs. 27%)[25]. Among patients infected with strain 027, bezlotoxumab in combination with actoxumab had a large treatment effect compared to bezlotoxumab alone (recurrent rates: 12 vs. 24%). Additionally, the rates of initial clinical cure were 80% with bezlotoxumab alone, 73% with actoxumab plus bezlotoxumab, and 80% with placebo; the rates of sustained cure (initial clinical cure without recurrent infection in 12 weeks) were 64%, 58%, and 54%, respectively.

Serious adverse events occurred in 29% of patients receiving bezlotoxumab and 33% of patients receiving placebo during the 12-week follow-up period, including heart failure, which was reported in 2.3% of bezlotoxumab and 1% of placebo recipients[26]. When compared to patients without heart failure at baseline prior to randomization to bezlotoxumab, patients with heart failure at baseline had numerically more adverse events (449/2019 (22.2%) vs. 99/325 (30.5%)), serious adverse events (168/2019 (8.3%) vs. 63/325 (19.4%)), and death (33/2019 (1.6%) vs. 23/325 (7.1%)). Therefore, the use bezlotoxumab in patients with heart failure should be reserved when the benefit outweighs the risk. In regards to immunogenicity, none of the patients who received bezlotoxumab in MODIFY I and II tested positive for treatment-emergent anti-bezlotoxumab antibodies[26].

A subset of patients from the MODIFY II trial (n = 295), were included in a 12 month extension study. At 12 months, fewer bezlotoxumab treated patients experienced recurrent CDI compared to patients treated with bezlotoxumab plus actoxumab and placebo (16.% vs. 21.4% and 42.7%, respectively). Additionally, colonization rates of *C. difficile* in the stool at months 6, 9, and 12 was similar among all patients that provided a stool sample, ranging from 16.3% to 32.4%[27].

Fecal Microbiota Transplantation

Fecal Microbiota Transplantation (FMT) involves introducing bacteria from a healthy donor into an individual with CDI in hopes of restoring gut microbiota leading to resolution of symptoms[28-29]. A liquid suspension of stool from a healthy donor is instilled into the GI tract of a CDI patient. Data suggest there are slightly higher rates of disease resolution with related donors compared to unrelated donors (93 vs. 84%)[30].

Evaluation of Clinical Efficacy and Safety

There are currently five published RCTs reporting the use of FMT in patients with recurrent CDI yielding a total of 434 patients. Van Nood, *et al*[31]. Conducted an open-label, RCT comparing FMT (via nasoduodenal tube) to oral vancomycin 500 mg QID for 14 days plus or minus bowel lavage in patients with recurrent CDI (1-9 prior CDIs). Patients that were randomized to FMT received oral vancomycin for 4 to 5 days followed by a bowel lavage prior to FMT administration. A total of 43 patients were randomized; however, the study was stopped early due to high relapse rates in both the control groups. Clinical cure occurred in 15 of 16 patients (94%) in the FMT group. Of those, 13 (81%) achieved a cure following single donor feces infusion. Lower rates of cure occurred in the vancomycin group (4/13 [31%]) and vancomycin plus bowel lavage (3/13 [23%]). Overall FMT was statistically superior to both vancomycin regimens in terms of cure ($p < 0.01$ after first infusion and $p < 0.001$ for overall cure rate). Fecal bacteria diversity increased following infusion of FMT resulting in microbiota diversity similar to a healthy donor.

Cammarota and colleagues[32] conducted an open-label RCT in 39 patients with recurrent CDI (median recurrence of CDI:3). Patients were randomized to receive FMT via colonoscopy or oral vancomycin 125 mg QID for 10 days followed by a pulse regimen for at least 3 weeks. Patients that received FMT were given oral vancomycin for 3 days followed by a bowel lavage prior to FMT administration. Thirteen of the 20 patients (65%) randomized to the FMT group achieved a cure (no recurrence within 10 weeks of FMT) following a single administration of FMT. Pseudomembranous colitis was identified in the remaining 7 patients. Six of the 7 patients received multiple infusions of FMT, with 5 patients achieving a cure. The overall cure rate was 90% (18/20 patients) in the FMT group; two patients died from apparent CDI complications. The vancomycin group had a lower cure rate with only 5/19 patients (26%) achieving a cure. Of the remaining 14 patients, two died from complications from CDI and 12 had CDI recurrence. Therefore, FMT resulted in significantly higher remission rates of recurrent CDI compared to vancomycin ($p < 0.0001$).

A double-blind, RCT of FMT was conducted by Kelly and colleagues[33] in patient's ≥ 3 recurrences of CDI and treatment with oral vancomycin for the most recent CDI. A total of 46 patients were randomized to receive FMT via colonoscopy with donor stool (heterologous) or patient's own stool (autologous). In the ITT analysis, 20/22 patients (91%) in the heterologous FMT group achieved clinical cure (no recurrence within 8 weeks) compared to 15/24 patients (63%) the in autologous group. The use of heterologous FMT was statistically superior to autologous FMT ($p = 0.024$). The 9 patients in the autologous group that had recurrence achieved clinical cure following the single administration of heterologous FMT. This resulted in an overall cure rate for heterologous FMT of 94% (29/31 patients). Microbiome analyses showed that heterologous FMT resulted in normalization and restoration of diversity of fecal microbiota. Whereas, microbial diversity did not result following autologous FMT.

The efficacy of FMT using frozen suspension from unrelated donors administered via colonoscopy or nasogastric tube (NGT) was evaluated in an open-label, RCT in 20 patients with recurrent CDI[34]. Resolution of disease (no relapse within 8 weeks) occurred in 14 patients (70%) following single administration of FMT. There was no significant difference between treatment groups: 8/10 in the colonoscopy group (80%) and 6/10 in the NGT group (60%; $p = 0.628$). Of the 6 patients that did not achieve a cure, five patients requested retreatment via NGT administration. One patient refused further treatment; however, the authors reported that this patient self-administered homemade fecal enemas (roommate donor) daily for a week and reported resolution of symptoms. Four of the five obtained cure following second infusion of FMT, resulting in an overall cure rate of 90%. Additionally, route of administration made no difference in the

microbiota composition and diversity following infusion.

Lee, *et al*[35] conducted a double-blind RCT in 232 patients with recurrent or refractory CDI to determine whether frozen-and-thawed FMT was noninferior to fresh FMT in terms of clinical efficacy. The proportions of patients with primary clinical resolution was similar in the frozen FMT group compared to the fresh FMT group (83.5 vs. 85.1%, treatment difference -1.6%, 95% 1-sided CI -10.5% to ∞, p = 0.01 for non inferiority). Additionally, there were no observed differences in adverse events between treatment groups.

Discussion

One of the most challenging aspects of CDI is its tendency to recur. Patients treated with first-line therapies, such as metronidazole and vancomycin, have exhibited recurrence of symptoms after effective treatment of CDI. Additionally, these therapies have been associated with microbiota damage which can cause long-term detrimental effects in terms of colonization resistance and overall microbiota health. Ridinilazole and cadazolid have generally been perceived as safe and effective in phase II trials; however, the majority of patients enrolled in these trials had no history of recurrent CDI and higher prevalence of non-severe CDIs. Phase III trials are required to determine their effects in a larger population and place in therapy for treatment of severe, complicated or recurrent CDI. In terms of treatment, bezlotoxumab did not have a superior effect over placebo for initial clinical cure, likely limiting its FDA approval to prevention of recurrent CDI. Phase III data suggest that bezlotoxumab, when used in combination with standard of care antibiotics, provides protection against recurrent CDI for potentially up to 12 months compared to placebo. Bezlotoxumab was also effective in patients with high risk of recurrent CDI, patients older than 65 years, considered immunocompromised, or considered to have severe CDI. Safety data suggest that bezlotoxumab should be reserved for use when the benefit outweighs the risk in patients with congestive heart failure. FMT has shown to have improved cure rates in patients with recurrent CDI compared to oral vancomycin. However, the data is limited to relatively small, open-label trials in patients with multiple recurrence of CDI. Large, well-design RCTs with long-term follow-up are needed to capture the efficacy and safety of FMT.

There are a number of promising agents currently in development that could provide new options for treatment and reduction of recurrent CDI. These agents have generally been perceived as safe and effective in phase II and III trials. However, continued research and publication is necessary to determine their roles in routine treatment and secondary prevention of CDI.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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