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Update on Treatment of *Clostridioides difficile* Infection

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Abstract

Clostridioides difficile infection (CDI) is the leading cause of health care–associated infections in the United States. The increasing incidence and recurrence rates of CDI together with its associated morbidity and mortality are great concerns. Newer treatment methods, such as narrow-spectrum antibiotics, monoclonal antibodies, and microbial replacement therapies, are being developed and implemented. We searched PubMed to identify published literature from 2010 to 2018 using the following keywords: *Clostridium difficile*, treatment, and therapy. Cited references were also used to identify relevant literature. This review focuses on the current standard of therapy and emerging therapies for CDI and summarizes the updated guidelines on treatment of CDI.

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Clostridioides difficile, a toxin-producing anaerobic bacterium, is the leading cause of health care–associated infection in the United States: An estimated 453,000 cases occur each year, and approximately 83,000 recurrences and 29,300 deaths are associated with *C difficile* annually.[1] The economic burden of *C difficile* infection (CDI) is estimated to be $4.8 billion in excess medical costs.[1,2] A large proportion of CDI is community-acquired infection, but the incidence and recurrence rates of CDI are increasing both in health-care settings and the community.[3,4] The diagnosis and management of recurrent CDI (rCDI) continue to be clinically challenging.

Recent developments have resulted in important changes in the recommendations for treatment of both initial CDI and rCDI. We searched PubMed to identify published literature from 2010 to 2018 using the following keywords: *Clostridium difficile*, treatment, and therapy. Cited references were also used to identify relevant literature. This review outlines the updated guidelines and recent developments in the management of CDI.

TREATMENT PRINCIPLES

The initial management of CDI includes classification of disease severity, fluid resuscitation, and correction of electrolyte abnormalities as needed. It is pertinent to stop unnecessary antibiotics because they are associated with longer time to resolution of diarrhea and with higher rates of complications, including rCDI.[5] Early diagnosis of CDI is essential in implementing isolation measures to curb transmission. Contact precautions should be implemented during treatment of patients who have suspected or confirmed CDI.[6,7] In routine clinical settings, hand hygiene should be maintained with soap and water or an alcohol-based hand hygiene product before and after contact with a patient who has CDI; however, *C difficile* spores are resistant to alcohol, so hand washing with soap and water may be more effective for infection control in hyperendemic settings.[8,9] The most recent Infectious Diseases Society of America (IDSA) guidelines suggest considering terminal room cleaning with a sporicidal agent, although the recommendation is weak.[9] In times of CDI outbreak, daily sporicidal disinfection may also be considered.

CLASSIFYING CDI SEVERITY

Classifying the severity of CDI may be helpful for selecting appropriate antibiotic therapy. Table 1 summarizes CDI severity criteria from the American College of Gastroenterology (ACG), the IDSA, and the European Congress of Clinical Microbiology

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and Infectious Diseases (ECCMID).[9-11,13] In clinical practice, CDI in a patient who meets one or more of the severity criteria outlined in any of these guidelines should be classified as severe CDI. Mild or moderate disease is classified as diarrhea with no signs of severe or fulminant infection.

ARTICLE HIGHLIGHTS

- Current pharmacologic and nonpharmacologic therapies for *Clostridioides difficile* infection (CDI) are reviewed.
- Investigational therapies for CDI are introduced.
- A treatment algorithm is provided for different severities of CDI and recurrences of CDI.

ANTIBIOTIC THERAPY

Although not approved by the US Food and Drug Administration (FDA) for CDI, metronidazole was recommended as first-line therapy for mild to moderate CDI in the older IDSA (2010)[13] and current ACG (2013)[10] and ECCMID (2009 and 2014)[11,12] guidelines (500 mg orally 3 times daily for 10 to 14 days) (Figure). However, recent data suggest that metronidazole is less effective than oral vancomycin in these patients. In one randomized trial, metronidazole had similar efficacy as vancomycin overall but was inferior in severe CDI.[14] Furthermore, metronidazole use may be associated with higher recurrence rates compared with vancomycin.[15-17] Adverse effects of metronidazole include peripheral neuropathy, nausea, and, with concurrent alcohol use, a disulfiram-like reaction that includes nausea and a metallic taste. Metronidazole is not recommended for women who are pregnant or breastfeeding and should not be used in the elderly or in patients with comorbidities.

Given all these concerns, in the updated IDSA guidelines released in February 2018, metronidazole is recommended for an initial episode of mild or moderate CDI only if vancomycin or fidaxomicin is not available.[9] If metronidazole is used and symptoms do not improve within 5 to 7 days, or if clinical signs worsen at any point, a change to vancomycin or fidaxomicin should be considered.[10] Intravenous metronidazole is indicated in fulminant CDI along with vancomycin (orally or rectally or both) (Table 2).[9-11]

Vancomycin is FDA approved for treatment of CDI. The standard therapy for nonfulminant CDI is vancomycin 125 mg orally 4 times a day for 10 days, but oral vancomycin is poorly absorbed, resulting in limited systemic exposure and high concentrations in the stool. Higher doses are not recommended except for fulminant infection. Oral vancomycin is also available in a liquid form (which is less expensive than pills) that was approved by the FDA in January 2018. In addition, some pharmacies are able to compound the intravenous form for oral administration.

Fidaxomicin is an oral macrocyclic antibiotic with minimal systemic absorption, a narrow spectrum of activity against gram-positive aerobic and anaerobic bacteria, and less impact on the normal bowel flora.[18,19] Post hoc analyses from a randomized clinical trial comparing fidaxomicin and vancomycin demonstrated that fidaxomicin showed more microbiome preservation than vancomycin.[20] Fidaxomicin is bactericidal against *C difficile*; metronidazole and vancomycin are bacteriostatic agents.[21]

In two randomized, phase 3 clinical trials, fidaxomicin was non-inferior to vancomycin for clinical cure (88.2% vs 85.8%; 91.7% vs 90.6%, respectively) and led to fewer recurrences (15.4% vs 25.3%; 12.7% vs 26.9%, respectively).[22,23] The updated IDSA guidelines recommend treatment with either vancomycin or fidaxomicin for an initial episode of nonfulminant CDI. For treatment of cancer patients, fidaxomicin was superior to vancomycin, with higher cure rates and fewer recurrences.[24] In a randomized controlled trial, extended-pulsed fidaxomicin (200 mg twice daily for days 1 to 5 and once daily on alternate days on days 7 to 25) compared with standard-dose vancomycin was found to be superior for sustained cure.[25] The rate of rCDI with this extended-pulsed fidaxomicin regimen was 4% compared to 17% for vancomycin at 30 days after the end of treatment.

Despite this evidence on the efficacy of fidaxomicin, its use has been limited in clinical practice, largely because of its high

TABLE 1. Summary of CDI Severity Classification From ACG, IDSA, and ECCMID Guidelines[a]

CDI severity[b]	ACG 2013[10]	IDSA 2017[9]	ECCMID 2009[11] and 2014[12]
Mild or moderate (nonsevere)	Diarrhea and no signs or symptoms meeting criteria for severe or fulminant CDI	WBC $<15\times10^9$/L and serum creatinine <1.5 mg/dL	Stool frequency <4 times daily No signs of severe colitis
Severe	Serum albumin <3 g/dL and 1 of the following: WBC $\geq15\times10^9$/L Abdominal tenderness	Leukocytosis (WBC $\geq15\times10^9$/L) or serum creatinine >1.5 mg/dL	Fever >38.5°C Rigors Hemodynamic instability
Fulminant	Any of the following attributable to CDI: ICU admission Hypotension Fever ≥38.5°C Ileus Mental status changes WBC $\geq35\times10^9$/L or $<2\times10^9$/L Serum lactate >2.2 mmol/L End organ failure	Hypotension or shock Ileus Megacolon	Peritoneal signs Ileus WBC $>15\times10^9$/L Marked left shift Increase in serum creatinine (≥1.5× baseline) Elevated serum lactate

[a]ACG = American College of Gastroenterology; CDI = *Clostridioides difficile* infection; ECCMID = European Congress of Clinical Microbiology and Infectious Diseases; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; WBC = white blood cell count.
[b]ECCMID 2014 guidelines classify CDI into only two groups according to severity: nonsevere and severe.

cost,[26,27] which has led some providers to recommend using fidaxomicin only in patients who have had multiple rCDIs. For example, in a multicenter, retrospective, observational study of fidaxomicin use at any US Department of Veterans Affairs medical center, the criteria for fidaxomicin use included CDI recurrence despite receiving two or more courses of oral vancomycin, including a tapered or pulsed regimen. Even with these criteria, fidaxomicin was used in less than 2% of patients with CDI.[28] However, in a multicenter retrospective review of all patients with CDI who were treated with fidaxomicin from 2011 to 2015, response rates decreased and recurrence rates increased with each subsequent CDI episode, suggesting that fidaxomicin is more efficacious when used earlier in CDI management.[29] In a recent study, the most cost-effective CDI treatment strategy was the following: for nonsevere initial CDI, fidaxomicin; for severe CDI, vancomycin; for first recurrence, fidaxomicin; and for subsequent recurrence, fecal microbiota transplant (FMT).[30]

A treatment algorithm based on the new IDSA guidelines is provided in the Figure, and a summary of the treatment guidelines from the three societies is outlined in Table 2. We recommend use of the IDSA guidelines because they are more recent than those from the ACG or ECCMID.

MANAGEMENT OF FULMINANT CDI

Patients with fulminant CDI have high mortality and morbidity.[10] They should be evaluated for megacolon and perforation with plain films of the abdomen or computed tomography of the abdomen and pelvis. High dose of vancomycin (500 mg orally 4 times a day) in combination with metronidazole (500 mg intravenously every 8 hours) is the preferred treatment (Figure). In a single-center, retrospective, observational study, mortality was lower among critically ill patients with CDI who received intravenous metronidazole in addition to vancomycin compared with patients who received vancomycin alone (15.9% vs 36.4%, P=.03).[31] If patients have ileus or colonic diversion, rectal vancomycin (500 mg in 100 mL of normal saline) may be added to these treatments.[10,13,32] Early surgical consultation for fulminant disease should also be considered.[10] Surgical therapy should be a consideration for patients with persistent shock, end-organ failure, mental status changes, white blood cell count greater than 50×10^9/L, lactate greater than 5 mmol/L, or failure to improve after 5 days of antibiotic therapy.[10,33]

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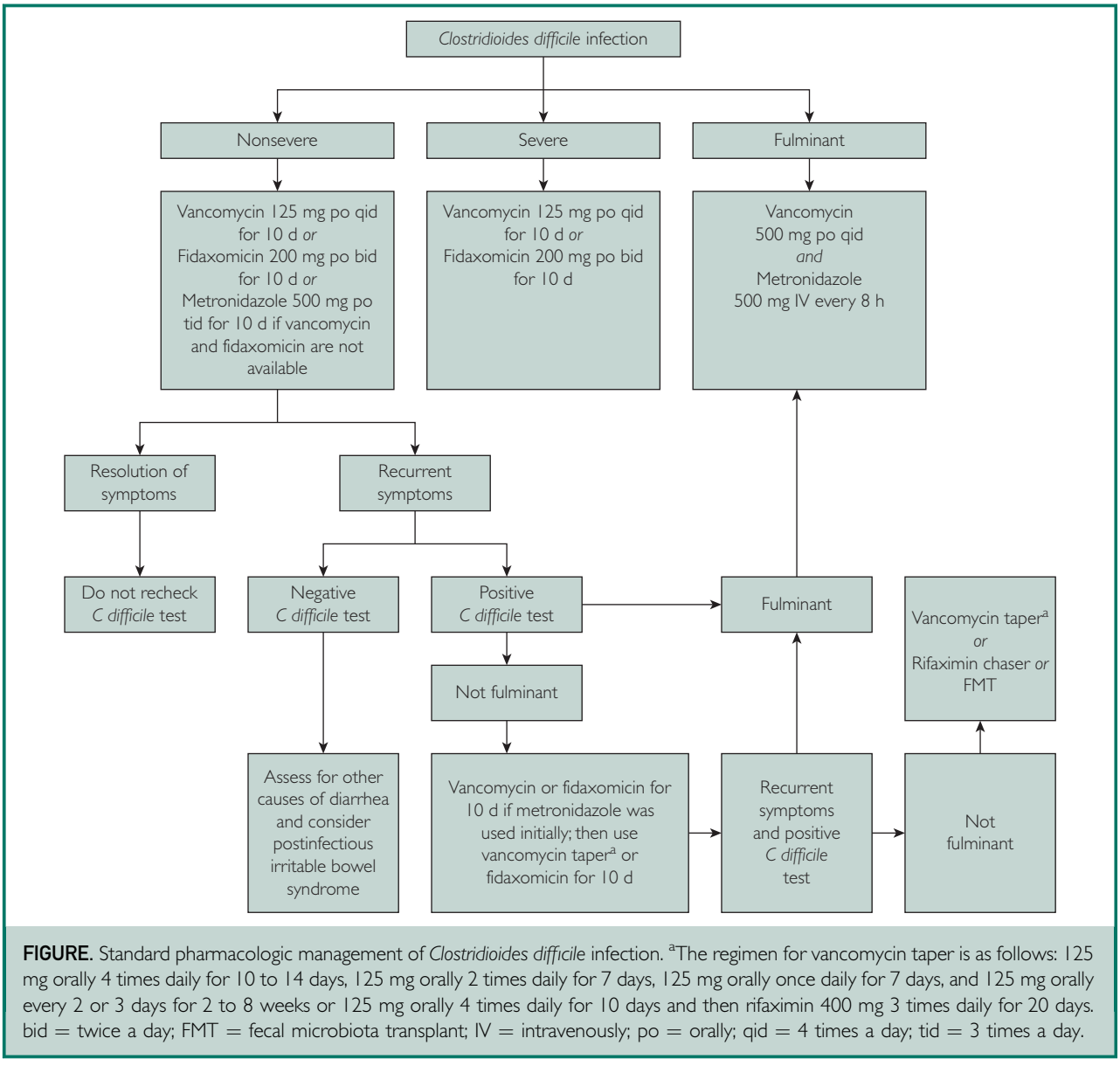

FIGURE. Standard pharmacologic management of *Clostridioides difficile* infection. [a]The regimen for vancomycin taper is as follows: 125 mg orally 4 times daily for 10 to 14 days, 125 mg orally 2 times daily for 7 days, 125 mg orally once daily for 7 days, and 125 mg orally every 2 or 3 days for 2 to 8 weeks or 125 mg orally 4 times daily for 10 days and then rifaximin 400 mg 3 times daily for 20 days. bid = twice a day; FMT = fecal microbiota transplant; IV = intravenously; po = orally; qid = 4 times a day; tid = 3 times a day.

In a retrospective, observational study of 165 patients who had CDI and required intensive care unit admission, the patients who underwent emergency colectomy had lower mortality than those who were treated with antibiotics alone (adjusted odds ratio [OR], 0.22; P=.008).[34] The optimal surgical intervention is not clear. In a study involving 42 patients with fulminant CDI, mortality was less among patients who underwent diverting loop ileostomy and colonic lavage with vancomycin compared with patients who underwent colectomy (19% vs 50%; OR, 0.24; P=.006).[35] In that study, the colon was preserved in 93% of the patients who underwent ileostomy and lavage, indicating that diverting loop ileostomy with colonic lavage may be a useful alternative to total colectomy. Despite those encouraging data, the World Society of Emergency Surgery guidelines recommend total colectomy for patients with fulminant colitis.[33]

MANAGEMENT OF CDI RECURRENCE

rCDI is defined as recurrence of symptoms and a positive test for *C difficile* within 8 weeks after completing therapy. It is important to consider

TABLE 2. Summary of Standard Pharmacologic Therapy According to CDI Severity and Recurrence From ACG, IDSA, and ECCMID Guidelines[a,b]

CDI severity[c] or recurrence	IDSA 2017[10]	ACG 2013[9]	ECCMID 2009[11] and 2014[12]
Mild or moderate	Vancomycin 125 mg qid ×10 d or Fidaxomicin 200 mg bid ×10 d or Metronidazole 500 mg tid ×10 d if vancomycin and fidaxomicin are not available	Metronidazole 500 mg tid ×10 d If unable to take metronidazole, vancomycin 125 mg qid ×10 d If no improvement in 5-7 d, consider changing to vancomycin (dosing as above)	Metronidazole 500 mg tid ×10 d If oral therapy is impossible, metronidazole 500 mg IV tid ×10 d
Severe	Vancomycin 125 mg qid ×10 d or Fidaxomicin 200 mg bid ×10 d	Vancomycin 125 mg qid ×10 d	Vancomycin 125 mg qid ×10 d If oral therapy is impossible, metronidazole 500 mg IV tid ×10 d, intracolonic vancomycin (500 mg in 100 mL of normal saline) every 4-12 h with or without vancomycin 500 mg qid by nasogastric tube
Fulminant	Vancomycin 500 mg qid and Metronidazole 500 mg IV every 8 h For complete ileus, consider adding vancomycin per rectum	Vancomycin 500 mg qid and Metronidazole 500 mg IV every 8 h and Vancomycin per rectum (500 mg in 500 mL of normal saline) qid	
First recurrence	Vancomycin 125 mg qid ×10 d if metronidazole was used initially Fidaxomicin 200 mg bid ×10 d or prolonged vancomycin taper (as below) if vancomycin was used initially	Treat with same regimen used for initial episode If severe, use vancomycin	Vancomycin 125 mg qid ×10 d or Fidaxomicin 200 mg bid ×10 d
Second or subsequent recurrences	FMT after ≥2 recurrences Vancomycin taper: 125 mg qid ×10-14 d, 125 mg bid ×7 d, 125 mg daily ×7 d, and 125 mg every 2 or 3 d for 2-8 w or Fidaxomicin 200 mg bid ×10d or Vancomycin 125 mg qid ×10d and then rifaximin 400 mg tid ×20 d	Vancomycin 125 mg qid ×10 d and then 125 mg daily pulsed every 3 d for 10 doses Consider FMT after third recurrence	Vancomycin 125 mg qid ×10 d and then consider pulsed-tapered strategy Consider FMT after third recurrence

[a]ACG = American College of Gastroenterology; bid = twice a day; CDI = *Clostridioides difficile* infection; ECCMID = European Congress of Clinical Microbiology; FMT = fecal microbiota transplant; IDSA = Infectious Diseases Society of America; IV = intravenously; qid = 4 times a day; tid = 3 times a day.

[b]Route of administration is oral unless indicated otherwise.

[c]ECCMID 2014 guidelines classify CDI into only two groups according to severity: nonsevere and severe.

that there are limitations to different modalities of *C difficile* testing. Polymerase chain reaction for the toxin genes *tcdA* or *tcdB* has high sensitivity but does not distinguish cases from carriers and can lead to overdiagnosis. Testing for glutamate dehydrogenase by enzyme immunoassay with subsequent testing of toxins A and B by enzyme immunoassay if positive, while able to detect active toxin production, has low sensitivity and may lead to missed cases.[9]

The 2017 IDSA guidelines recommend treating a first recurrence with oral vancomycin as a tapered and pulsed regimen or a 10-day course of fidaxomicin rather than a second 10-day course of vancomycin if vancomycin was used initially.[9] If metronidazole was used for the initial infection, a 10-day course of vancomycin is recommended.

In a study of patients with rCDI, patients who received a standard 10- to 14-day course of vancomycin had recurrence rates up to

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54%; those who received tapering regimens, 31%; and those who received pulsed regimens, up to 14%.[36] The mechanism for why pulsed regimens of vancomycin seem more efficacious than tapered regimens is not known, but perhaps a contributing factor is that the intestinal flora can regenerate during the times vancomycin is not given.[36] (See Table 2 for a pulsed vancomycin regimen.) More recently, in a study of patients with rCDI treated with a vancomycin taper, 41% had another recurrence.[37] Although these recurrence rates are lower than expected for patients with multiple recurrent infections (approximately 60%),[38] they are not lower than the recurrence rates after FMT (see below), suggesting that a vancomycin taper is not ideal therapy for preventing rCDI in these patients.

In a randomized, double-blind, placebo-controlled study, patients with CDI were randomly assigned to receive rifaximin 400 mg 3 times daily or placebo for 20 days after finishing standard CDI therapy. In the rifaximin group, 21% experienced recurrent diarrhea compared with 49% in the placebo group (P=.02). However, the CDI recurrence rate between the two groups was not statistically different (15% in the rifaximin group vs 31% in the placebo group, P=.11).[39] The updated IDSA guidelines recommend a rifaximin chaser for second or subsequent recurrences[9] (see Table 2).

In a randomized, stratified substudy comparing fidaxomicin and a standard 10-day course of vancomycin in patients with a first CDI recurrence, fidaxomicin therapy was associated with a lower rate of recurrence (19.7% vs 35.5%, P=.04).[40] In a study of patients who received fidaxomicin for treatment of CDI, the rate of rCDI was 0% for patients with a first episode of CDI, 23% for patients with one previous episode, and 29% for patients with at least two previous episodes; those results suggest that fidaxomicin may be less efficacious in patients with a history of recurrences than in patients with a first infection.[29]

Given these data, better treatments are needed for patients with rCDI, especially those who have had two or more recurrences. For those patients, FMT is recommended for correcting the microbiome disruption caused by repeated antibiotic therapy[9,10] (see below). Therapy for rCDI is summarized in Table 2.[10,11,13]

All data on oral vancomycin prophylaxis (OVP) are from retrospective studies. In a retrospective cohort study of patients with rCDI, the recurrence rate was 54.4% among patients who received OVP and 69.5% among those who did not (P<.001).[41] In another retrospective study, the recurrence rate was 4.2% among patients who received OVP and 26.6% among those who did not.[42] A Canadian retrospective study showed that among 20 patients who received OVP for at least 8 weeks, only one relapse occurred during 200 patient-months of follow-up.[43] In a study of renal transplant patients who received broad-spectrum antibiotics, no patient who received both OVP and antibiotics had a recurrence, whereas 8% of patients who received only antibiotics had recurrences, but the difference was not statistically significant (P=.54).[44] In a retrospective cohort study of patients undergoing allogeneic hematopoietic cell transplant, none of the patients who received OVP had CDI, but among patients who did not receive OVP, 20% had CDI (P<.001).[45] Currently no guidelines recommend OVP, but it may be beneficial to institute OVP in patients who are immunocompromised and receiving systemic antibiotic therapy.

MICROBIAL REPLACEMENT THERAPIES

Antibiotic therapy disrupts the normal gut flora and its ability to prevent *C difficile* colonization, proliferation, and toxin production, which increases the risk of primary CDI and rCDI.[1] Understanding the central role of this antibiotic-induced dysbiosis in the pathogenesis of CDI, and particularly in rCDI, has led to the development of several microbial replacement therapies.

FMT has been the primary method for providing microbial replacement therapy for treating rCDI. In a 2017 systematic review, which included seven randomized controlled trials and 30 case series, clinical resolution occurred in 92% of patients treated with

FMT.[46] FMT is administered by various methods, including nasogastric and nasoduodenal tube, colonoscopy, and enema. In a study from the Netherlands, 81% of patients had resolution of rCDI after a single duodenal fecal infusion compared with 31% in the vancomycin group.[47] In other observational and controlled studies, FMT by colonoscopy resulted in a 91% primary cure rate.[48,49] Outcomes do not appear to be different between use of fresh or frozen stool.[50,51] In a randomized single-center trial in Denmark involving 64 patients, clinical resolution of CDI was seen more frequently in patients treated with FMT after 4 to 10 days of vancomycin (92%) than among patients treated with vancomycin (42%) or fidaxomicin (19%) for 10 days without FMT.[52]

A limited amount of literature discusses the use of FMT for treatment of refractory severe CDI. In one case series of four patients, FMT provided short-term improvement but long-term outcomes were variable.[53] A case series of nine patients showed 100% symptom resolution, with recurrence in one patient who was receiving antibiotics.[54] In a larger study, the response to a treatment protocol of sequential FMT and continued use of vancomycin guided by clinical response was 100% for patients with severe CDI and 89% for patients with fulminant CDI.[55] Ongoing clinical trials are assessing the use of FMT as a primary treatment of moderate to severe CDI, the use of FMT or antibiotic therapy for initial treatment of rCDI, and the use of different modes of delivery for FMT, such as by capsule. We recommend FMT for prevention of further recurrences in patients who have had three or more episodes of CDI, with consideration of FMT in patients who have had two episodes of CDI, especially if the episodes were severe or severe-complicated.

ENEMA-BASED MICROBIAL REPLACEMENT

RBX2660 (Rebiotix, Inc), a microbiota-based suspension derived from donor stool, is being studied in clinical trials for treatment of rCDI. Data from an open-label phase 2 trial showed that RBX2660 administered by enema was superior to placebo with no adverse effects; 51.6% of patients had a response after the first treatment, and 78.6% who received a second treatment had a response, with an overall response rate of 87.1%.[56] In a blinded phase 2b multicenter, placebo-controlled randomized trial, the primary endpoint studied was the response to RBX2660 or placebo at 8 weeks. Two doses of RBX2660 were not superior to two doses of placebo (61% vs 45.5%, $P=.15$). However, evaluation of the secondary endpoint showed that two doses of RBX2660 were more effective than one dose of placebo for resolution of rCDI (64% vs 46%, $P=.047$).[57] In a third phase 2 study, RBX2660 met the primary endpoint of preventing CDI recurrence at 8 weeks, with a success rate of 78.8% compared with 51.8% ($P<.001$) in historical controls treated with antibiotics alone.[58] Phase 3 studies are under way.

CAPSULE-BASED THERAPIES

SER-109 (Seres Therapeutics, Inc) is an oral capsule that contains spores derived from stool of healthy donors. In an exploratory study, 30 patients with rCDI were treated with SER-109 after they had a therapeutic response with oral antibiotics; CDI resolved in 96.7%.[59] Gut microbial diversity increased significantly as early as day 4. In addition to the growth of organisms included in SER-109, non—SER-109 bacteria also increased in prevalence. For example, *Bacteroides*, a dominant bacterium in healthy persons that was not present in the SER-109 product, was augmented in 38% of patients. Also, after SER-109 administration, the prevalence of some pathogens decreased. For example, *Klebsiella* carriage had decreased by 92% by week 4. Adverse effects included mild diarrhea, abdominal pain, and nausea.[59] However, a phase 2 study did not show that SER-109 was superior to placebo (44% of patients in the SER-109 group had rCDI compared with 53.3% in the placebo group; the difference was not statistically significant).[60] A phase 3 multicenter, randomized, double-blind, placebo-controlled trial is under way (Clinicaltrials.gov NCT03183128; Seres Therapeutics, Inc).

CP101 (Finch Therapeutics) is an oral capsule containing full-spectrum microbiota

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derived from donor stool. It is being investigated in a phase 2 double-blind, placebo-controlled, dose-finding trial in patients with rCDI (Clinicaltrials.gov NCT03110133).

RBX7455 (Rebiotix, Inc) is a lyophilized, broad-spectrum gut microbiota preparation in a room-temperature–stable oral capsule. A single-center, three-arm phase 1 clinical trial of RBX7455 for treatment of rCDI is under way (Clinicaltrials.gov NCT02981316).

SER-262 (Seres Therapeutics, Inc) is a fermentation-derived, rationally designed, oral microbiome therapeutic that contains bacteria from clades in healthy persons. The ability of SER-262 to prevent a first recurrence of CDI after appropriate antibiotic therapy for primary CDI was assessed in a recently completed phase 1b trial. VE303 (Vedanta Biosciences, Inc), an orally administered live bacterial consortium in powder form, is undergoing assessment for prevention of rCDI in a phase 2 clinical trial.

ANTIBODY-BASED TREATMENTS

The humoral immune response against *C difficile* toxins is an important determinant of patient outcomes. Higher serum concentrations of antibodies against toxin A have been associated with a decreased risk of CDI recurrence risk.[61] In a prospective study, asymptomatic carriers had greater levels of antibodies against toxin A compared with patients who had *C difficile*–associated diarrhea.[62] As discussed below, administration of pooled immunoglobulin may help to treat active infection and decrease the risk of rCDI. More recent evidence indicates that use of a monoclonal antibody against *C difficile* toxins is an effective adjunctive treatment.

Bezlotoxumab

Bezlotoxumab is a monoclonal antibody that binds to *C difficile* toxin B and is FDA approved as an adjunctive therapy for preventing CDI (in addition to providing standard of care with antibiotics) in adults at high risk for recurrence. It is not approved for use as a stand-alone therapy. In two double-blind, randomized, placebo-controlled, phase 3 trials (MODIFY I and MODIFY II), patients receiving bezlotoxumab in combination with standard oral antibiotic therapy had significantly lower rates of rCDI than patients treated with antibiotics alone (17% vs 28% in MODIFY I; 16% vs 26% in MODIFY II).[63] Bezlotoxumab did not affect initial response rates and had a similar safety profile compared with placebo. The choice of antibiotic therapy (metronidazole, vancomycin, or fidaxomicin) for CDI did not influence outcomes in either group.

A recent study used a computer-based Markov health state transition model to investigate the cost-effectiveness of adding bezlotoxumab to standard therapy to reduce the recurrence of CDI. The model predicted that adding bezlotoxumab would reduce first recurrence by 10.1%, the total number of recurrences by 16.7%, and 180-day mortality by 1.1%. The study also showed that concurrent use of bezlotoxumab with standard CDI antibiotics was cost-effective.[64] A recent post hoc analysis showed that, compared with placebo, bezlotoxumab reduced rCDI rates in patients who had five pre-specified risk factors (age $\geq$65 years, history of CDI, immunocompromised state, severe CDI, and ribotype 027, 078, or 244). The absolute reduction was −14.2% for patients with one risk factor, −14.2% with two risk factors, and −24.8% with three or more risk factors.[65] These results suggest that in certain subgroups of patients, bezlotoxumab may be particularly cost-effective.

Intravenous Immunoglobulin

Pooled intravenous immunoglobulin likely has *C difficile* antitoxin and has been used as an adjunctive therapy to antibiotics in severe and refractory CDI.[66] Limited data exist on the benefits of this therapy, and an uncontrolled, retrospective study involving 18 patients showed no difference in mortality, colectomy, and length of hospital stay between standard therapy and intravenous immunoglobulin adjunctive therapy.[67]

PROBIOTICS AND NONTOXIGENIC *C DIFFICILE*

Probiotics are micro-organisms that can provide a health benefit to the host.[68] These have been studied for the prevention and treatment

of CDI with conflicting results. In a 2006 meta-analysis, *Saccharomyces boulardii*, which can cause fungemia in certain hosts, was efficacious for preventing *C difficile*–associated diarrhea when administered in combination with standard antibiotics in adults with prior antibiotic exposure (relative risk, 0.59; 95% CI, 0.41-0.85; *P*=.005).[69] However, in another meta-analysis, probiotics (including *Saccharomyces*) were not effective for treating CDI as adjunctive therapy.[70] For CDI prevention, a 2016 meta-analysis of 26 randomized controlled trials found that *Lactobacillus*, *Saccharomyces*, and a mixture of probiotics reduced the risk of CDI in adults and children treated with antibiotics in inpatient and outpatient settings (relative risk reduction: 63.7% with *Lactobacillus*, 58.5% with *Saccharomyces*, and 58.2% with a mixture of probiotics).[71] Overall, probiotic use reduced the risk by 60.5% (relative risk, 0.395; 95% CI, 0.294-0.531; *P*<.001). The absolute risk reduction is 2.3% (number needed to treat, 43 patients). However, more research is needed because of the heterogeneity between studies in these meta-analyses.

In a phase 2 randomized, double-blind, placebo-controlled trial, patients with CDI who had responded to oral antibiotics were administered nontoxigenic *C difficile* strain M3 (NTCD-M3) orally.[72] Those patients had a significantly smaller risk of rCDI compared with patients who were given placebo (2% vs 31%; OR, 0.01; 95% CI, 0-0.05; *P*<.001), and NTCD-M3 had a better safety profile than placebo, suggesting that this novel organism could be used as a probiotic to prevent rCDI. Confirmatory phase 3 studies are awaited.

Investigational Pharmacologic Therapy

Ridinilazole is a novel, nonabsorbable, narrow-spectrum antimicrobial that targets *C difficile*. The mechanism of action has not been fully elucidated, but it may have a role in impairing cell division.[73] In a randomized, phase 1 study, gut microbiota analysis showed minimal changes apart from a reduction in the total number of *C difficile* organisms, which were undetectable by day 4 of ridinilazole use.[74] In a phase 2 multicenter, randomized, double-blind, non-inferiority study of patients with rCDI, 66.7% of patients who received ridinilazole and 42.4% who received vancomycin had a sustained clinical response (treatment difference, 21.1%; 90% CI, 3.1-39.1; *P*=.004), establishing the non-inferiority of ridinilazole and also showing statistical superiority at the 10% level.[75] Phase 3 confirmatory studies have been started.

CONCLUSION

The increasing incidence and recurrence rates of CDI continue to cause considerable patient suffering and mortality and an enormous economic burden. Emerging therapies, including FMT, other microbiome-based therapies delivered through various routes of administration, and novel antimicrobials are being developed and tested in clinical trials and may be available soon as additional therapeutic options for patients with CDI. The future of CDI treatment will likely include the development of antibiotics that have narrower spectra and are less disruptive to the microbiome, the emergence of vaccines for CDI, the use of early microbial replacement through various routes, and the development of defined microbial consortia.

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Abbreviations and Acronyms: **ACG** = American College of Gastroenterology; **CDI** = *Clostridioides difficile* infection; **ECCMID** = European Congress of Clinical Microbiology and Infectious Diseases; **FDA** = US Food and Drug Administration; **FMT** = fecal microbiota transplant; **IDSA** = Infectious Diseases Society of America; **OR** = odds ratio; **OVP** = oral vancomycin prophylaxis; **rCDI** = recurrent *Clostridioides difficile* infection

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