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Management of *Clostridioides difficile* colitis: insights for the gastroenterologist

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Abstract: *Clostridioides difficile* infection (CDI) is a common cause of diarrhea in both inpatient and outpatient settings. The last few years have seen major changes in the treatment spectrum of CDI, most notably, recommendations against using metronidazole for initial CDI, the addition of fidaxomicin and bezlotoxumab, and emergence of microbial replacement therapies. Several other therapies are undergoing clinical trials. This narrative review focuses on the treatment of CDI with a summary of literature on the newer modalities and the treatment guidelines issued by Infectious Diseases Society of America and European Society of Clinical Microbiology and Infectious Diseases.

Keywords: *Clostridioides difficile*, *Clostridium difficile*, *C. difficile* diarrhea, fecal microbiota transplantation

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Introduction

Clostridioides difficile (previously *Clostridium difficile*) is the most common pathogen implicated in healthcare-associated infections in the United States (US).[1] Recent data suggest that ~40% of *C. difficile* infections (CDIs) in the US are community-associated, which often do not have risk factors such as antibiotic exposure or hospitalization commonly associated with healthcare-associated CDI.[2] In Europe, the incidence of CDI is lower than in the US.[3,4] It is the eighth most frequently reported microorganism in healthcare-associated infections, with increasing incidence in most countries; the majority of cases (76.4%) are healthcare-associated.[5,6]

CDI classically presents with watery diarrhea (Bristol stool scale 6–7, three or more times a day) and crampy abdominal pain, with or without fever. In rare cases with ileus or a megacolon, diarrhea may not be present. Diagnosis is made by a positive stool test in the presence of typical clinical features. A gamut of tests is available, and the choice of test depends on the institutional protocol and test availability.

Management of CDI has changed significantly in the last few years, with several new treatment options available. In this article, we describe the treatment of primary and recurrent CDI in adults as recommended by recent guidelines along with investigational therapies for CDI.

Classification of CDI episodes

Prior to starting treatment for CDI, it is essential to grade the severity of the episode, and also note whether there were prior episodes. CDI is classified as mild-to-moderate, severe or fulminant (earlier termed severe-complicated) based on laboratory parameters and clinical features. The commonly used criteria for classification are as follows[7,8]:

- Severe disease is diagnosed in the presence of white blood cell (WBC) count $> 15{,}000 \times 10^6$/l, or creatinine rise >1.5-times baseline or >1.5 mg/dl
- Fulminant disease is diagnosed when there is hypotension, shock, sepsis, intensive care unit admission, megacolon, perforation or colectomy due to CDI
- Mild-to-moderate disease is diagnosed when the criteria for severe or fulminant disease are not met.

Several other classification criteria have been used to determine severity [ATLAS, American College

of Gastroenterology (ACG) 2013, European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2014 criteria and others], though none have been accepted universally.[9–11] Most of these scores are based on expert opinion. Validation studies have yielded variable results, though acute kidney injury and leukocytosis have consistently predicted severe disease.[11–15] Large, well conducted prospective validation studies are needed to shed light on the best criteria for use in clinical practice.

The earlier guideline from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) from 2010 recommended different treatments based on severity of the episode, thus requiring the use of laboratory tests (e.g. WBC, creatinine) as a guide to treatment. The updated guideline recommends the same treatment for mild-to-moderate and severe episodes, no longer mandating these tests as a part of the initial evaluation of a patient. The ESCMID guidelines retain the need for severity criteria in guiding treatment options.

The first episode of CDI in a patient is termed primary CDI. Recurrent CDI is defined as recurrence of typical symptoms within 8 weeks of the previous episode, with documented symptom resolution in the interim. Physicians need to be careful when interpreting stool tests in the context of a possible recurrence. Nucleic acid amplification tests (NAATs) often remain positive following successful treatment of a prior episode. This is because they are highly sensitive and can detect small quantities of the toxin gene in the stool.

Updates on testing

The updated IDSA/SHEA 2017 guideline recommends a multistep algorithm with a stool toxin test when there are no institutional protocols for stool specimen submission.[7] The algorithm uses a glutamate dehydrogenase (GDH) test plus toxin, toxin plus NAAT, or GDH plus toxin arbitrated by NAAT. Where there are predefined stool submission protocols, a single NAAT, or a toxin test as part of multistep algorithm can be used. The caveat is to test only on unformed stools in patients with watery diarrhea $\geqslant$3 times in 24 h. There is no role of repeat testing in case of an initial negative test, unless there is a change in the clinical presentation or in epidemic settings; test of cure post-treatment is also not recommended.[7]

The ESCMID guidelines also support a two-step algorithmic approach to diagnosis.[16] They suggest using either GDH or NAAT for screening, followed by reflex testing of positive samples with toxin A/B enzyme immunoassay (EIA). Samples with a negative second test may be tested with NAAT (if not used before) or toxigenic culture. An alternative approach is to use a combination of GDH and toxin A/B EIA for screening; samples with concordant results can be reported as such. Samples with a negative GDH and positive toxin test should be retested with NAAT or toxigenic culture. Repeat testing should be avoided for initial positive results, and no test of cure is recommended; initial negative results can be retested if there is ongoing clinical suspicion during an epidemic situation or when there is high suspicion during endemic situations.[16]

In situations where a patient tests positive for *C. difficile* but does not have the typical symptoms, a positive test represents an asymptomatic carrier who needs no further treatment. The clinical picture is often further complicated when patients have diarrhea after a prior CDI episode, with or without a positive stool test. Studies have shown that ~25% patients develop post-infectious irritable bowel syndrome following an episode of CDI.[17,18]

Management

All inpatients with CDI should be isolated; infection control measures should be initiated and continued till discharge. Concomitant acid suppressant medications and opioid medications increase the risk of severe disease and should not be used.[19] Systemic antibiotics herald a poor outcome and increase recurrences, hence must be discontinued when possible. Continued proton pump inhibitor (PPI) use also increases the risk of recurrence, hence should be stopped.[20,21]

Antimicrobial treatment

The healthy human gut is host to a diverse microbiota which protects it from pathogenic bacteria by competitive exclusion and production of bacteriocins. When this microbial milieu is perturbed ('gut dysbiosis'), the host becomes susceptible to infections. In order to develop CDI, both gut dysbiosis

and colonization with *C. difficile* bacterium are predisposing factors. The ideal therapeutic agent for CDI is one that successfully kills the bacterium while restoring the disrupted gut microbiota.

Several drugs are used to treat CDI, each with its own spectrum of activity, efficacy, and toxicities. Metronidazole is the oldest drug used for CDI treatment, although it is not recommended by the United States (US) Food and Drug Administration (FDA) for this purpose and is not recommended by the 2017 IDSA/SHEA guideline in most situations.[7,22] It is a broad-spectrum antibiotic used to treat anaerobic infections. Metronidazole kills the vegetative forms of the *Clostridioides* bacterium but not the spores.[23] Thus, it terminates the infection, but leaves the patient susceptible to recurrences in the face of persistent or renewed risk factors for CDI. Metronidazole is almost completely absorbed in the small intestine with undetectable levels in the feces of healthy adults.[24] In the presence of diarrhea however, the levels of the drug in feces increase; this is likely due to the decreased transit time and secretion of the drug across an inflamed colonic mucosa.[24,25] Since it is absorbed from the gut, systemic side effects are of concern when repeated or prolonged courses are used.

Vancomycin is another commonly used drug for CDI. While its use in other infections is *via* the intravenous (i.v.) route, for CDI it is given as an oral suspension or liquid formulation. In this form, it achieves high concentrations in the stool, well above the minimum inhibitory concentration (MIC) required for its action (MIC_{90} for *C. difficile* is 1–2 mg/l).[26] Although higher doses achieve higher fecal concentrations, even 125 mg dose achieves 500–1000 times the MIC_{90}, which is adequate for clinical efficacy.[26] However, the major drawbacks to its use are the propensity to select antibiotic-resistant forms of other bacteria present in the gut.[27] Additionally, like metronidazole it is not sporicidal, leaving the patient vulnerable to recurrences.[23]

Fidaxomicin is a macrocyclic antibiotic with narrow spectrum of activity. It kills the vegetative form of *C. difficile* bacteria, and binds to its spores, preventing them from germinating and producing toxin[23,28] It also causes less disruption of the gut microbiota compared with vancomycin.[29] However, studies exploring its effect on the gut microbiota are on patients with CDI and not healthy humans. Since patients with CDI already have a disrupted microbiota, the clinical utility of this nondisruptive effect is questionable.

Rifaximin is a broad-spectrum, gut selective antibiotic used for the treatment of conditions such as hepatic encephalopathy and small bowel overgrowth. It has good *in vitro* activity against *C. difficile* and has been primarily used after a course of standard antibiotics.[30] In large clinical trials, rifaximin did not meet the non-inferiority definition for cure of CDI.[30–32] It is recommended in the IDSA/SHEA guidelines to use as a chaser regimen after vancomycin for recurrent CDI.[7] Its use in CDI is not recommended by the US FDA.

Treating the first episode

Prior to the year 2000, two randomized controlled trials (RCTs) found similar cure rates for metronidazole and vancomycin for treating CDI.[33,34] However, these were small trials with <50 patients in each arm. More recently, three RCTs, with a total of 687 patients, found vancomycin to be superior to metronidazole in terms of cure rates.[35,36] The two RCTs with a total of 1105 patients comparing fidaxomicin with vancomycin found similar cure rates for both drugs, but with lower recurrence rates in patients treated with fidaxomicin.[37,38]

On the basis of these studies, the IDSA/SHEA 2017 guideline recommends vancomycin [125 mg four times daily (QID) per oral (PO) for 10 days] or fidaxomicin [200 mg twice daily (BID) PO for 10 days] for the first mild-to-moderate/severe episode of CDI.[7] Metronidazole [500 mg three times daily (TID) for 10 days] is recommended for the initial mild-to-moderate episode only if the first-line drugs are not available. This was a change from the previous guideline, wherein metronidazole (for mild-to-moderate) and vancomycin (for severe) were recommended for the first episode of CDI.[8] The evidence supporting these recommendations is of high quality, leading to a strong recommendation for all regimens except metronidazole, which has a weak recommendation.[7]

The 2014 ESCMID guidelines recommend several options for the initial nonsevere episode.[39] These include metronidazole (500 mg TID for 10 days; class IA recommendation), vancomycin (125 mg QID for 10 days; class IB recommendation), fidaxomicin (200 mg BID for 10 days; class

Table 1. Treatment of recurrent *Clostridioides difficile* infection (IDSA/SHEA 2017 guideline).[7]

Indication	Treatment recommended	Treatment regimen	Strength of recommendation/ quality of evidence
First recurrence	Vancomycin (if treated with metronidazole before)	125 mg QID PO for 10 days	Weak/low
	Fidaxomicin (if treated with vancomycin before)	200 mg BID PO for 10 days	Weak/moderate
	Tapered and pulsed vancomycin (if treated with vancomycin standard regimen before)	125 mg QID for 10–14 days, 125 mg BID for a week, 125 mg OD for a week, and then 125 mg every 2 or 3 days for 2–8 weeks	Weak/low
Second or subsequent recurrence	Tapered and pulsed vancomycin	125 mg QID for 10–14 days, 125 mg BID for a week, 125 mg OD for a week, and then 125 mg every 2 or 3 days for 2–8 weeks	Weak/low
	Fidaxomicin	200 mg BID for 10 days	Weak/low
	FMT	FMT dosage, route etc. is not standardized	Strong/moderate
	Vancomycin followed by rifaximin chaser	Vancomycin 125 mg QID PO for 10 days; rifaximin 400 mg TID PO for 20 days)	Weak/low

BID, twice daily; FMT, fecal microbiota transplantation; IDSA, Infectious Diseases Society of America; OD, once daily; PO, per oral; QID, four times daily; SHEA, Society for Healthcare Epidemiology of America; TID, three times daily.

IB recommendation), vancomycin (500 mg QID for 10 days; class IC recommendation), or observation for 48 h after stopping the inducing antibiotic (class IIC recommendation). If oral administration is not possible, i.v. metronidazole can be given (class IIA recommendation). The major difference is the recommendation for using metronidazole by ESCMID, which was changed in the IDSA/SHEA guideline following publication of complete results of the RCTs.[35]

Treating recurrences

For the treatment of the first recurrence, the IDSA/SHEA guideline recommends a different regimen than what was used in the first episode (Table 1). For the second or subsequent recurrence, there are several options (Table 1). The evidence supporting these recommendations is of low to moderate quality, leading to a weak recommendation for all regimens except fecal microbiota transplantation (FMT). The ESCMID guideline recommends oral vancomycin or fidaxomicin for the first recurrence, with a marginal strength of recommendation for using metronidazole (Table 2). For multiply recurrent CDI, FMT is strongly recommended; vancomycin (taper or pulse regimen) and fidaxomicin are given a moderate strength of recommendation, and metronidazole is not recommended (Table 2).

Antibiotic regimens

Vancomycin taper/pulse regimen has not been extensively evaluated in recurrent CDI; in one study with 163 patients, a vancomycin taper/pulse lowered recurrence rates.[36] However, a recent retrospective study in over 900 patients found no difference between vancomycin with and without taper regimen in terms of recurrence at 90 or 180 days.[37] They also failed to find a mortality benefit of using a taper regimen. The patient population consisted predominantly of males, with a majority experiencing their first recurrence. There is a lack of consensus regarding the best dosing for the pulse/taper regimen; a recent study found lower recurrence rates when pulse dose was given to once every other followed by once every third

Table 2. Treatment of recurrent *Clostridioides difficile* infection (ESCMID 2014 guideline).[34]

Indication	Treatment recommended	Treatment regimen	Strength of recommendation/ quality of evidence
First recurrence (or risk of recurrence)	Vancomycin	125 mg QID PO for 10 days	IB
	Fidaxomicin	200 mg BID PO for 10 days	IB
	Metronidazole	500 mg TID for 10 days	IC
	Vancomycin	500 mg QID PO for 10 days	IIIC
Multiply recurrent CDI	Fecal or bacterial instillation	Vancomycin, 500 mg QID for 4 days with bowel lavage and nasoduodenal infusion of donor feces	IA
	Vancomycin pulse	125 mg QID for 10 days, followed by 125–500 mg OD every 2–3 days for ⩾3 weeks.	IIB
	Vancomycin taper	125 mg QID for 10 days, gradually decreasing to 125 mg OD	IIB
	Fidaxomicin	200 mg BID for 10 days	IIB
	Vancomycin	500 mg QID PO for 10 days	IIC
	Metronidazole	500 mg TID for 10 days	IID (recommendation against use)

BID, twice daily; CDI, *Clostridioides difficile* infection; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; OD, once daily; PO, per oral; QID, four times daily; TID, three times daily.

day as compared with once every other day only.[38] The duration of taper is also not standardized; a retrospective study suggested a longer duration was associated with a lower recurrence rate.[39]

The recommendation for using fidaxomicin for recurrent CDI comes from a subgroup analysis of patients included in the two phase III RCTs of fidaxomicin. Out of the total 1164 patients included in the trials, 128 patients who were enrolled for treatment of their first recurrence of CDI were included in this study. The study found comparable cure rates, but lower recurrence rates (19.7%) with fidaxomicin compared with a 10 day vancomycin regimen (35.5%) within 4 weeks of treatment.[40] In an observational study, the recurrence rate after fidaxomicin treatment was 22% (within 4 weeks) or 19% (within 8 weeks) depending on the definition used.[41] The patient population consisted primarily of those with two or more prior episodes, and the recurrence rate increased sequentially with the number of prior CDI episodes. A recent RCT studied the efficacy of fidaxomicin, FMT and vancomycin in 64 patients with multiply recurrent CDI; the primary outcome was a composite of clinical resolution and a negative *C. difficile* polymerase chain reaction test at the end of 8 weeks.[42] They found FMT (by colonoscopy or nasojejunal tube after 4 days of vancomycin) to be superior to both fidaxomicin and vancomycin, and fidaxomicin and vancomycin to be comparable (the primary outcome achieved in 71%, 33% and 19% patients given FMT, fidaxomicin and vancomycin respectively). Recurrence within or after 8 weeks of treatment was seen in 8.3% of FMT, 45.8% of fidaxomicin, 68.7% of vancomycin-treated patients.[42] This is a statistically significant difference between FMT and both antibiotics, and a comparable recurrence rate with fidaxomicin and vancomycin. The cure rates seen in this study are much lower, and the rate of recurrence is much higher than in the two previous studies; this could be due to the patient population which had a higher number of prior CDI episodes, and hence a higher baseline risk for recurrence.[40,41] The small number of patients included could be another factor. This RCT supports findings from the observational study in

which recurrence rates increased with the number of prior CDI episodes.[41] More high-quality evidence is needed to provide better recommendations for this high-risk patient population.

Rifaximin is used as a chaser post-vancomycin for recurrent CDI. Efficacy data are limited; an RCT with 68 patients and found a lower rate of all-cause diarrhea, but not recurrent CDI-related diarrhea when compared with the placebo arm.[26] The inclusion criteria were limited to patients with primary or one prior CDI episode, thus limiting applicability in multiply recurrent CDI. A recently published RCT with 151 patients found a statistically nonsignificant reduction in recurrence with rifaximin *versus* placebo following an episode of CDI.[25] Other small open-label trials and retrospective studies found rifaximin to be comparable to standard therapies, but with highly heterogeneous study characteristics.[27] Data from ongoing trials are awaited (ClinicalTrials.gov identifier: NCT01670149).

Other options such as a fidaxomicin taper course after standard treatment of recurrent CDI are being explored and have shown to be promising in small studies.[43] The premise of such therapies is to control the *C. difficile* bacterial load in the colon, while giving time for colonization resistance to be re-established. The principle is similar to vancomycin taper regimens, with the added benefit of the narrow-spectrum activity of fidaxomicin minimizing additional gut dysbiosis. Details regarding microbial replacement for multiply recurrent CDI are given in the following section.

Overall, there is a lack of high-quality evidence for the management of the first recurrence of CDI; large, well conducted prospective studies are needed in the future to overcome this knowledge gap.

Microbial replacement therapies

FMT is a novel, highly effective therapy for treatment of CDI, with cure rates of over 80% in most clinical trials.[44,45] It is based on the principle that restoration of a healthy gut microbiota will reduce susceptibility of a patient to CDI. At present, FMT is primarily used to treat recurrent CDI, though it is sometimes used for antibiotic refractory disease as well. In cases where there is the need for ongoing systemic antibiotics, FMT is delayed until after they can be stopped. Patients are kept on antibiotics (usually vancomycin or fidaxomicin) to control symptoms, until 24–72 h prior to the procedure; following FMT, antibiotics for CDI are not restarted. Mild, self-limited diarrhea is common after the procedure.[46] Of note, the FDA has not approved FMT, but has allowed its use as an investigational drug.[47]

Since the first RCT established the efficacy of FMT in recurrent CDI, several others have followed and confirmed its efficacy.[35,48–50] Most trials have shown high cure rates (>80%), though meta-analyses show somewhat lower cure rates in controlled (67.7%) *versus* open-label trials (82.7%) after a single FMT.[44,45] A concern with FMT is the lack of standardization of the procedure. There is a wide variability in all stages of the process: donor screening, donor type (related/unrelated, single/pooled, site-specific donors/stool banks), stool processing, volume of stool infused, specific stool product (whole stool/enriched), form (fresh/frozen/lyophilized), dose (single/multiple FMTs) and route of administration (oral/nasogastric/nasojejunal/enema/colonoscopy). The reporting of specific methods used is also inconsistent.[51] Data are accumulating for many of these variables; studies have shown fresh and frozen stool to be equivalent and lyophilized stool to be inferior in efficacy.[45,48,49] Overall, lower gastrointestinal (GI) routes are superior to upper GI routes in terms of efficacy (95% and 88% respectively), though enema has lower cure rates than colonoscopy (66% and 87% respectively).[44,45,52,53] In terms of safety, minor adverse events (AEs) are more frequent in the upper GI route while serious AEs (SAEs) are more frequent in the lower GI route (minor AEs, 43.6% *versus* 17.7; SAEs, 2% *versus* 6% in the upper and lower GI routes respectively).[46] In an RCT, oral capsules were as efficacious as colonoscopy, and with a more favorable safety profile.[50]

A small proof-of-principle RCT was done to assess the efficacy of FMT for treating primary CDI episode compared to metronidazole.[54] In this trial, 20 patients were included, and primary full response (clinical cure without recurrence at day 70) was achieved in both groups equally, suggesting that FMT could be an effective treatment option for the first episode. However, the study evaluated metronidazole, which is now proven to be less effective than other first-line treatment options.

Though most studies have focused on the bacterial composition of the stool and its role in the efficacy

of FMT, other components (nonbacterial organisms, bile acids and protein metabolites) may also have a role.[55,56] Careful exploration of these components may in the future lead to the development of a refined stool product, theoretically with a lower risk of AEs. Several microbiome-based therapeutics are in the pipeline (RBX7455, RBX2660, SER-109), with the hope of developing a standardized stool-based product.[57,58] RBX2660 is a microbiota-based suspension prepared from human stool (kept frozen, thawed before use and administered as an enema) currently undergoing a phase III trial (ClinicalTrials.gov identifier: NCT03244644). RBX7455 is an oral, room temperature stable, lyophilized microbial restoration therapy currently undergoing a phase I trial (ClinicalTrials.gov identifier: NCT02981316). SER-109 is an oral capsule containing different bacterial spores produced from purified, enriched human stool; it is currently undergoing phase III clinical trials (ClinicalTrials.gov identifiers: NCT03183128, NCT03183141). Development and approval of these microbiome-based products would reduce the heterogeneity of product administered while improving ease of administration and accessibility.

Despite the lack of standardization of stool processing methods and FMT procedure, multiple studies have proven the efficacy of FMT.[44,45] The major issue at present is the scarcity of long-term safety data. Data from systematically followed up patients and registries, such as that set up by the American Gastroenterological Association (AGA), would go a long way in providing this much needed information.

Preventing recurrences

Antibody treatments

Several therapeutic modalities (e.g. an antibody against *C. difficile* toxins, nontoxigenic *C. difficile* spores, vaccines) are being evaluated for the prevention of recurrent CDI (secondary prevention). The two multicenter phase III RCTs (MODIFY I and MODIFY II) looked at the efficacy of monoclonal antibodies actoxumab (against toxin A) and bezlotoxumab (against toxin B) in preventing the recurrence of *C. difficile*.[59] The study enrolled 2655 patients; the primary endpoint was recurrent CDI during 12 weeks of follow up. Actoxumab infusion alone was stopped after interim analysis due to higher rates of recurrence and more serious AEs. Initial cure rates were similar across groups. Bezlotoxumab and bezlotoxumab-actoxumab combination groups had a lower recurrence than placebo (decrease of 10.1% in MODIFY I and 9.9% in MODIFY II for bezlotoxumab alone; decrease of 11.6% and 10.7% in MODIFY I and II respectively for combination therapy). There was no difference between bezlotoxumab alone *versus* combination therapy in terms of the primary endpoint. These results held true in patients with a higher risk of recurrence. In 2016, the US FDA approved bezlotoxumab for preventing CDI recurrences in adults receiving antibiotics for the infection and with a high risk of recurrence. However, in the two trials conducted, only 4% patients were on fidaxomicin, and none received FMT as their standard of care. Considering the efficacy of these two therapies in preventing recurrences, the role of this drug in the real-world setting is yet undefined.

Nontoxigenic C. difficile

Nontoxigenic *C. difficile* spores protect against the colonization by toxigenic strains and halt the development of CDI; a phase II trial found very low (2%) recurrence rate within 6 weeks of treatment in patients colonized with nontoxigenic *C. difficile* spores.[60] Phase III trials are warranted to elucidate the role of this treatment option in preventing CDI.

Are there data for vancomycin prophylaxis to prevent CDI?

Data on the efficacy of vancomycin as a CDI prophylaxis are emerging.[61–63] A study in 551 adult patients found vancomycin to be effective as a secondary but not primary prophylaxis, with a >50% decrease in risk of recurrent CDI.[64] The protective effect was seen in patients receiving the prophylaxis for >50% duration of the antibiotic therapy; the most frequent dose used was 125 mg QID. Another study in 203 adults with prior CDI found CDI in 4.2% and 26.6% in those who did and did not receive secondary vancomycin prophylaxis.[63] The follow-up period was 1 month, and vancomycin was given as 125 mg or 250 mg BID. These studies were limited by their retrospective design, limited follow up, heterogeneous duration and dose of therapy, and inability to study the effect of vancomycin on the bowel flora. Additionally, none of them reported on the occurrence of vancomycin-resistant *Enterococci* infections, which is a major

concern with vancomycin prophylaxis. Considering the risks of using vancomycin (propagation of gut dysbiosis, selection of resistant organisms), the lack of high-quality evidence and the availability of other effective preventive strategies, at present, vancomycin prophylaxis should be used after a careful risk–benefit discussion.

Vaccines

Several vaccines against *C. difficile* are being developed and are currently undergoing clinical trials (ClinicalTrials.gov identifiers: NCT01887912, NCT02316470, NCT02117570, NCT02561195). This could be an effective approach in select high-risk populations, decreasing cost, morbidity and mortality for the patient. Other therapies such as ribaxamase (a beta lactamase inhibitor) are being studied.

Treating severe and severe-complicated (fulminant) disease

For the treatment of fulminant CDI, a high dose of vancomycin [500 mg QID both PO and per rectal (PR)] in addition to metronidazole (500 mg TID i.v.) is recommended by the IDSA/SHEA guideline.[7] Evidence supporting this recommendation is limited to observational studies and case series.[65–67] These studies support the use of i.v. metronidazole in addition to vancomycin therapy. The addition of a vancomycin enema in cases with gut discontinuity or slowed transit (such as colectomy or ileus) is scientifically sound. For other cases however, data are limited and equivocal. Heterogeneity in defining severe disease also complicates the interpretation of these results. Hypothetically, use of a higher dose of vancomycin can be used to counteract the effect of slowed gut transit (in patients with ileus) which can affect fecal concentrations of the drug, although no pharmacokinetic studies have evaluated this particular subgroup of patients.

The ESCMID guideline recommends a 10 day course of oral vancomycin (125 mg QID, IA recommendation) or fidaxomicin (IB); vancomycin dose can be increased to 500 mg QID (IIIB).[34] Use of metronidazole is strongly discouraged (I–D) for severe CDI. Intravenous metronidazole (500 mg TID for 10 days; IIA recommendation) with vancomycin retention enema (500 mg in 100 ml normal saline QID intracolonic), or with vancomycin PO/nasogastric tube (500 mg QID for 10 days; IIIB recommendation) can be given. For fulminant CDI, early colectomy is recommended.[34]

Other therapies have been evaluated for the treatment of severe/severe-complicated disease. A small study including 57 patients with severe (n = 19) and severe-complicated CDI (n = 38) found high cure rates with FMT in both groups (100% and 91% respectively).[68] FMT was given when there was no response to 5 days of PO/PR vancomycin and i.v. metronidazole therapy; single or multiple FMTs were delivered through sigmoidoscopy/colonoscopy, with one patient undergoing an enema. Another case series with 17 patients found a cure rate of 88% with FMT.[69]

A small observational study found intravenous tigecycline (loading dose of 100 mg followed by 50 mg BID) as adjunct therapy to be marginally favorable to metronidazole-vancomycin therapy in terms of mortality.[70] Tigecycline monotherapy was superior in terms of progression to complicated disease and clinical cure when compared with combination therapy in a retrospective study with 90 patients.[71] A matched study did not find a difference in cure or recurrence when tigecycline was added to vancomycin therapy[72]; another study found no mortality benefit when it was added to standard of care in a patient cohort primarily comprising of severe-complicated CDI.[73]

A recent study with 287 patients found oral teicoplanin to be superior to oral vancomycin in severe or severe-complicated CDI, both in terms of cure as well as recurrence rates.[74] Studies looking at alternative treatment options such as polyethylene glycol (PEG) instillation are underway, and would provide much needed insights.[75] The use of i.v. immunoglobulin remains controversial with no large observational or randomized studies yet.[76,77]

For patients who do not respond to medical treatment, present with acute abdomen, have a rising lactate/WBC, or worsening clinical condition (organ failure, shock, sepsis), surgery is necessary. Overall, less than 1% of patients with CDI require a colectomy, but with a high associated mortality of ~30%.[78] The procedure of choice is subtotal colectomy with end ileostomy. Leukocytosis and lactate levels have consistently been shown to predict worse outcomes post-surgery, while early surgery is protective.[79,80]

An alternative strategy using diverting loop ileostomy with colonic lavage decreased mortality while preserving the colon.[81,82] However, recent data from over 400 patients in a surgical database found no difference in mortality between loop ileostomy and total colectomy, though there was benefit in terms of colon preservation.[83] Despite the lack of high-quality evidence, it is prudent to say that early surgical consultation and careful monitoring of a patient's clinical condition are vital. The choice of surgical procedure remains controversial, though loop ileostomy is clearly beneficial in colon preservation.

CDI in inflammatory bowel disease

Management of CDI in patients with inflammatory bowel disease (IBD) can be particularly challenging. This is due to lower response to the usual antibiotics, propensity to develop severe/severe-complicated disease and an increased risk of recurrences.[84,85] CDI in these patients often lacks the typical risk factors such as antibiotic use, affects younger patients and is frequently community-acquired.[86,87] Occurrence of CDI increases the risk of adverse outcomes such as IBD flares, intensification of therapy for IBD, colectomy and death.[88,89] Due to the considerable overlap between clinical features of CDI and IBD, all patients with a suspected IBD flare should be tested for *C. difficile*.

Data regarding management of CDI in patients with IBD are limited. A study comparing vancomycin with metronidazole found a shorter length of stay and fewer readmissions with vancomycin in ulcerative colitis but not Crohn's disease.[90] In an open-label prospective study of 25 patients with CDI and IBD, fidaxomicin was found to be well tolerated, with cure rates of 80% and recurrence rate of 17%.[91] A post-approval study of fidaxomicin evaluated its use in special populations, including IBD.[92] They found similar resolution and recurrence rates in IBD and the general population with CDI at 2 and 6 months of follow up.[92] In another study, resolution or improvement of diarrhea occurred in all patients with CDI and IBD treated with fidaxomicin, with a recurrence rate of 19%.[41]

FMT is another therapy for patients with IBD and recurrent CDI, with cure rates of 74–85.7%, and possibly higher efficacy with repeat FMT.[93–95] A recent study found recurrence rates after FMT to be similar in IBD and non-IBD groups with CDI; PPI use, severe CDI and hypertension predicted recurrence at 6 months.[96] The risk of an IBD flare after FMT was 16%, which was lower than previous estimates, and there was no worsening of disease activity.[96,97] Considering the emerging data on efficacy of FMT in treating IBD, it is an attractive option for treating patients with CDI and IBD, though treatment regimens are different.[98,99]

The issue of immunosuppression in patients with CDI and IBD is another major concern. Studies on the role of immunosuppression in causing adverse outcomes (colectomy, readmissions, hospital readmissions and death) have yielded conflicting results.[90,100,101] Immunosuppression does not seem to affect the efficacy of FMT.[93,95,96]

To summarize, it seems prudent at this time to treat patients with CDI and IBD with vancomycin or fidaxomicin; FMT may be preferred in recurrent CDI. The decision regarding immunosuppression needs to be individualized. Above all, as patients with CDI and IBD are at an elevated risk of adverse outcomes, close monitoring and a low threshold for escalating therapy is essential. Ongoing clinical trials of FMT in this population will add much needed high-quality evidence (ClinicalTrials.gov identifiers: NCT03106844, NCT03829475).

Investigational therapies

Cadazolid and ridinilazole are new drugs with narrow-spectrum activity, high fecal concentrations and low systemic absorption. Both drugs were found to be well tolerated in phase II trials.[102,103] The primary cure rate was comparable, and sustained cure rate (primary cure with no recurrences) was higher for all doses of cadazolid than for vancomycin, primarily due to lower recurrence rates with cadazolid.[102] However, in one of the two phase III trials conducted (>600 patients in each), the primary endpoint was not achieved, and development of the drug was stopped (ClinicalTrials.gov identifiers: NCT01983683, NCT01987895).

In the published phase II trial of ridinilazole, primary cure was comparable and sustained cure (clinical cure with no recurrences within 30 days) was higher for ridinilazole than for vancomycin due to a lower recurrence rate.[103] Two large

multicenter phase III trials, Ri-CODIFY 1 and 2 are planned, and are expected to be completed by 2021 (ClinicalTrials.gov identifiers: NCT03595553, NCT03595566).

Surotomycin is a narrow-spectrum cyclic lipopeptide similar to vancomycin; two parallel multicenter phase III trials with over 570 patients each were conducted to evaluate surotomycin efficacy in CDI. While one trial demonstrated non-inferiority but not superiority over vancomycin, the other did not meet the non-inferiority criteria.[104,105] Given these findings, the development of surotomycin was stopped.

Primary prevention strategies

The most important strategies for preventing CDI are judicious antibiotic use and infection control practices, particularly during an outbreak. However, these measures are often inadequate, implausible or ineffective. Probiotics are often used concurrently with antibiotics to prevent antibiotic-associated diarrhea. The role of probiotics in preventing CDI has been extensively studied, with most studies demonstrating benefit, especially with earlier administration.[106,107] However, there is no consensus regarding the choice and dose of probiotic. Furthermore, despite a significant reduction (>50%) in CDI occurrence, the number needed to treat is high (>40), which may limit its value in clinical practice.

A recent retrospective study in 244 elderly (⩾65 years) patients looked at the efficacy of oral vancomycin prophylaxis (125 mg once daily) in primary prevention of CDI. Patients included were those who received systemic antibiotic therapy during hospital stay. CDI occurred during hospital stay in 0% and 10.4% patients in those who received prophylaxis *versus* those who did not[62]; another retrospective study found no benefit of vancomycin as a primary prevention strategy.[64]

Conclusion

The therapeutic landscape against CDI is rapidly evolving with accumulation of evidence from clinical trials and observational studies. At present, vancomycin and fidaxomicin are the drugs of choice in treating primary as well as recurrent CDI; the use of metronidazole is limited to severe-complicated disease. FMT should be offered to patients with multiply recurrent CDI. Further research into the treatment of recurrent and severe disease is warranted. Several drugs and microbiota-based products are undergoing clinical trials and may soon join the armamentarium available to physicians and patients to combat CDI.

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Conflict of interest statement

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