

***Clostridium difficile* infection: a review of current and emerging therapies**

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Abstract

Clostridium difficile (*C. difficile*) infection (CDI) is the most common cause of healthcare-associated infections in US hospitals. The epidemic strain NAP1/BI/ribotype 027 accounts for outbreaks worldwide, with increasing mortality and severity. CDI is acquired from an endogenous source or from spores in the environment, most easily acquired during the hospital stay. The use of antimicrobials disrupts the intestinal microflora enabling *C. difficile* to proliferate in the colon and produce toxins. Clinical diagnosis in symptomatic patients requires toxin detection from stool specimens and rarely in combination with stool culture to increase sensitivity. However, stool culture is essential for epidemiological studies. Oral metronidazole is the recommended therapy for milder cases of CDI and oral vancomycin or fidaxomicin for more severe cases. Treatment of first recurrence involves the use of the same therapy used in the initial CDI. In the event of a second recurrence oral vancomycin often given in a tapered dose or intermittently, or fidaxomicin may be used. Fecal transplantation is playing an immense role in therapy of recurrent CDI with remarkable results. Fulminant colitis and toxic megacolon warrant surgical intervention. Novel approaches including new antibiotics and immunotherapy against CDI or its toxins appear to be of potential value.

Keywords *Clostridium difficile* infection, fecal microbial transplantation, fidaxomicin, humanized monoclonal antitoxin antibodies, toxic megacolon

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Introduction

Clostridium difficile (*C. difficile*) is now widely recognized as the leading cause of nosocomial diarrhea worldwide with associated substantial morbidity and mortality [1,2]. Recent data suggest an increase in both the incidence and severity of *C. difficile* infection (CDI) [3]. Over 250,000 people need hospital care and at least 14,000 people die from CDI in the United States each year based on statistics from the Centers of Disease Control and Prevention [4].

The recent increase in incidence and severity is due to the emergence of the hypervirulent strain, NAP1/BI/ribotype 027 that is more resistant to antibiotics and produces more toxin [5-7]. CDI is most frequently caused by exposure to antibiotics, which alters the natural flora of the intestines [8]. Depletion of gut flora allows endogenous or environmental

C. difficile to proliferate in the colon and produce toxins. Meta-analyses of current data implicate clindamycin, cephalosporins, and fluoroquinolone antibiotics as the highest risk antibiotics [9-11]. CDI occurs particularly during the use of the antibiotic and within the first month after antibiotic use, but the risk persists for up to 90 days [12]. However, in community-acquired CDI patients, proton pump inhibitor exposure has been observed in about 31% of patients with CDI, with no exposure to antibiotics [13]. This review discusses the clinical features of CDI, diagnosis of *C. difficile* and highlights current and new emerging therapies for CDI.

Microbiology

C. difficile is an anaerobic toxin-producing gram-positive spore forming bacterium. Transmission is via the fecal-oral route. Colitis and diarrhea is mediated through the release of two exotoxins by *C. difficile*: toxin A ("enterotoxin") and toxin B ("cytotoxin"). Toxin A, causes increased intestinal permeability and fluid secretion. Toxin B, leads to intense colonic inflammation. Toxins bound to receptors gain intracellular entry by modification of Rho proteins-small glutamyl transpeptidase-binding proteins. These proteins are involved in actin polymerization, cytoskeletal architecture, and cell movement. The resultant effect is the loss of intercellular tight

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junctions leading to secretory diarrhea, and an inflammatory response with eventual cell death [14].

Clinical manifestations/diagnosis of CDI

The clinical presentation of CDI ranges from asymptomatic carriage, to mild or moderate diarrhea, to fulminant colitis [15,16]. Three or more watery, nonbloody stools per 24-h period is the hallmark of symptomatic illness [17]. Mild disease is characterized by diarrhea in the absence of signs and symptoms of colitis whereas moderate disease is characterized by moderate diarrhea with colitis manifested by fever, abdominal cramps and discomfort, usually in the lower quadrants [18]. Severe disease is characterized by white blood cell count of $>15,000$ cells/ μL , serum albumin <3 g/dL, and/or a serum creatinine level ≥ 1.5 times the premorbid level [19].

The clinical features of CDI/fulminant colitis include fever, diarrhea leading to hypovolemia, severe lower quadrant or diffuse abdominal pain, abdominal distention, severe lactic acidosis, hypoalbuminemia, and significant leukocytosis (40,000 white blood cells/ μL or higher) [20]. Fulminant colitis can lead to bowel perforation and toxic megacolon. Other complications of *C. difficile* include electrolyte imbalance, renal failure from severe dehydration, systemic inflammatory response syndromes and sepsis. Bacteremia is rare, with few case reports of *C. difficile* bacteremia [21]. Diagnosis is based on the presentation of signs and symptoms of CDI, with confirmed microbiological evidence of toxin-producing *C. difficile* in stools, or colonoscopic or histopathological findings of pseudomembranous colitis (PMC) particularly with the exclusion of other causes of PMC [22]. However, not all patients with CDI have pseudomembranes, particularly patients with mild or partially treated infection. There are reports of PMC caused by other organisms such as *Salmonella* [23]. The absence of pseudomembranes does not rule out CDI.

Laboratory diagnosis of CDI

CDI should only be investigated in patients with diarrhea. Diagnostic tests available include enzyme immunoassays (EIA) for toxins, EIA for *C. difficile* glutamate dehydrogenase (GDH) and nucleic acid amplification tests (NAATs, or Polymerase chain reaction (PCR) for *C. difficile* toxin genes. Other diagnostic tests include toxigenic cultures, or cell culture neutralization assays (CCNA) [24].

One strategy to improve sensitivity is through a two-step method that uses EIA detection of GDH as an initial screen. Antigen-positive specimens for GDH (and negative for toxin(s) if tested) are further assessed using a NAAT or CCNA [25]. Toxigenic culture is considered the gold standard, however its use limited in the clinical setting given the duration of time for culture results to become available. NAATs (e.g. PCR) are highly specific ($>95\%$), and highly sensitivity rapid tests for *C. difficile* detection. This diagnostic test affords a quick and efficient way of detecting CDI [26].

Imaging studies and procedures

Radiology

Radiographic findings are neither sensitive nor specific for CDI. Radiographic features on abdominal radiography suggestive of CDI include polypoid mucosal thickening, haustral fold thickening, or gaseous distention of the colon. Abdominal computed tomography scan findings include low-attenuation colonic mural thickening corresponding to mucosal and sub-mucosal edema, with wall thickening involving the entire colon (pancolitis), peri-colonic fat stranding, and ascites [27].

Endoscopy

Endoscopy is indicated when there is a high clinical suspicion for CDI with negative laboratory assay or when other colonic diseases are in the differential diagnosis (e.g. inflammatory bowel disease) [28]. Typically in negative laboratory assay, CDI is suggestive by the direct visualization of pseudomembranes on lower gastrointestinal endoscopy (either proctosigmoidoscopy or colonoscopy) or by histopathologic examination [22,29]. Pseudomembranes appear as raised, yellowish white, 2- to 10-mm plaques which overly an erythematous and edematous mucosa (Fig. 1).

Management of CDI

General principles

The inducing antibiotic(s) or other medications that predispose to CDI should be stopped as soon as possible, is a strong recommendation in the treatment of CDI [30]. Supportive care should include careful fluids and electrolyte

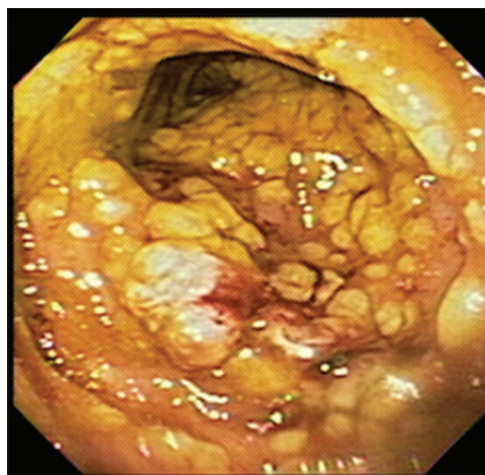


Figure 1 Endoscopic view of *Clostridium difficile*-induced pseudomembranous colitis. Yellow pseudomembranes attached to the colonic mucosa with friable erythematous colonic mucosa
Courtesy of Kenolisa Onwueme, MD, PhD

management. The use of anti-motility agents for CDI treatment is discouraged. Patients should be placed on contact precautions in all suspected CDI [19]. Hand hygiene with soap and water by healthcare providers, hospital visitors and patients is more potent than alcohol-based hand sanitizers in eliminating *C. difficile* spores, due to the inherent resistance of *C. difficile* spores to alcohol [31]. One time use of disposable equipment is recommended to prevent transmission of CDI. Sole use of non-disposable medical equipment in a patient with CDI with thorough cleaning after use is recommended [19]. In the event of a high clinical suspicion for CDI, medical therapy is recommended before laboratory confirmation [19].

Medical therapy

The choice of antibiotic therapy should be tailored to the severity of disease presentation.

- a. Mild-to-moderate disease:** The antibiotics metronidazole or vancomycin have been the initial treatment options for CDI. Recommended regimen is oral metronidazole 500 mg t.i.d. for 10-14 days. The use of intravenous metronidazole at a dose of 500 mg t.i.d. can also be used for treatment of CDI in lieu of oral therapy [32]. Oral vancomycin 125 mg q.i.d. for 10-14 days can be as used alternatively for non-severe CDI. Vancomycin is usually preferred in patients who are intolerant/allergic to metronidazole, pregnant and nursing mothers [19]. Failure to respond to metronidazole therapy within 5-7 days requires a change in therapy to standard dose of vancomycin (125 mg orally q.i.d.) [19,32], (Table 1).
- b. Treating severe or complicated CDI:** Prompt initiation of oral vancomycin, 125 mg q.i.d., for severely ill patients is critical. Some clinicians favor a higher dosing of vancomycin, 500 mg q.i.d., for severe disease [33]. Vancomycin may also be administered rectally as a retention enema in the setting

of ileus, megacolon, and colonic diversion [34]. Intravenous metronidazole is added as adjunctive therapy for ileus or severe/complicated CDI, typically with vancomycin when administered orally, or as a retention enema [35]. The use of fidaxomicin (200 mg orally b.i.d.) is a reasonable alternative in patients with severe disease with less clinical response to oral vancomycin. Fidaxomicin and vancomycin, have similar clinical cure rates; the OR (95%CI) was 1.17 (0.82-1.66) however sustained cure rates [1.75 (1.35-2.27)] are significantly higher for fidaxomicin than vancomycin with lower recurrence rate of fidaxomicin compared to vancomycin [0.47 (0.34-0.65)] [36]. The apparent superiority of fidaxomicin in the treatment of CDI is limited by the cost of therapy. There is also some limited data on the use of intravenous tigecycline as a rescue therapy for the treatment of patients with severe CDI, in whom therapy with vancomycin and metronidazole failed [37]. However, there are no randomized clinical trials to support this evidence. Early surgical consultation is warranted in severe complicated CDI. Surgery is recommended in the presence of peritoneal signs, severe ileus, and toxic megacolon. In a retrospective observational cohort study, immunocompetent patients aged ≥ 65 years with a white blood cell count $\geq 20,000$ cells/ μL and/or a plasma lactate >2.2 mmol/L had good clinical outcomes following colectomy [38].

Recurrence of *C. difficile*

Recurrent CDI is defined by the complete resolution of presenting symptoms on appropriate therapy, with subsequent relapse and return of symptoms within eight weeks of the initial episode completion of treatment [39]. About 10-20% of CDI recur after an initial episode of *C. difficile*, but when

Table 1 Recommendations from the ACG [19] and the ESCMID [22] for *Clostridium difficile* infection (CDI) treatment, based on the severity of disease

CDI severity	ACG Guidelines (2013) [19]	ESCMID Guidelines (2014) [22]
Mild-to-moderate disease	Metronidazole 500 mg PO t.i.d. 10 days If intolerant to metronidazole or if no improvement in 5-7 days of metronidazole therapy: vancomycin 125 mg PO q.i.d. for 10 days	Metronidazole 500 mg PO t.i.d. 10 days Alternatives: - Vancomycin 125 mg PO q.i.d. for 10 days - Fidaxomicin 200 mg PO bid 10 days
Severe disease	Vancomycin 125 mg PO q.i.d. for 10 days	Vancomycin 125 mg PO q.i.d. for 10 days Alternative: - Fidaxomicin 200 mg PO b.i.d. 10 days
Severe and complicated disease	Vancomycin 500 mg PO q.i.d. plus metronidazole 500 mg IV t.i.d. If ileus, toxic colon or significant abdominal distention: vancomycin 500 mg in 500 mL saline per rectum q.i.d. Surgical consultation/management in complicated disease; e.g. subtotal colectomy with ileostomy or diverting loop ileostomy and colonic lavage+antibiotic treatment	Vancomycin 125 mg PO q.i.d. for 10 days Alternative: - Fidaxomicin 200 mg PO bid 10 days Surgical consultation/management for complicated diseases- e.g. subtotal colectomy with ileostomy or diverting loop ileostomy and colonic lavage+antibiotic treatment
Recurrent disease	1 st recurrence: repeat the same antibiotic used for the initial episode (metronidazole or vancomycin, standard regimen) 2 nd recurrence: pulsed or tapered vancomycin regimen (see text) 3 rd recurrence: fecal microbiota transplant plus vancomycin	1 st recurrence: vancomycin or fidaxomicin (standard regimen) 2 nd recurrence: pulsed or tapered vancomycin regimen or fidaxomicin (standard regimen) 3 rd recurrence: fecal microbiota transplant plus vancomycin

Some data Adapted from: Carmo J, Marques S, *et al* [33]

a patient has had one recurrence, rates of further recurrences increase to 40-65% [40].

Impaired colonization resistance, allowing proliferation of *C. difficile* and impaired immune response demonstrated by lower levels of immunoglobulin G antibody to toxin A are thought to contribute to recurrence [41]. Other risk factors for recurrent disease include advanced age, additional courses of antibiotics and/or chemotherapy, use of medications such as proton pump inhibitors, prolonged hospital stay, and prior episodes of recurrent CDI [42]. There is evidence to show that a majority of recurrence of CDI is due to relapses of infection with the original strain rather than re-infection [43,44].

Management of initial recurrence

Both the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend treating the first recurrence of CDI with the same therapeutic agent used in the initial episode [22]. Metronidazole is preferred for the treatment of non-severe initial recurrence. The use of oral vancomycin should be based the severity of disease at the time of first recurrence rather than its use in prior CDI. Fidaxomicin dosed at 200 mg b.i.d. for 10 days is an alternative agent for treatment of an initial recurrence of CDI [45]. Fidaxomicin has similar efficacy to vancomycin in achieving a clinical response in patients with a first recurrence of CDI, however is exceptional in preventing a second recurrence within 28 days (19.7 versus 35.5%; 95%CI -30 to -0.3%); $P=0.045$) [46].

Management of subsequent recurrences of CDI

A second recurrence of CDI can be treated with fidaxomicin (200 mg b.i.d. for 10 days) or by a pulsed or tapping dose of oral vancomycin [47]. Intermittent and tapered vancomycin regimens have been evaluated in an observational study in a cohort of 163 with active recurrent CDI. Of the 163 cases, 44.8% had a recurrence of CDI. A tapering course of vancomycin yielded fewer recurrences (31%, $P=0.01$) as did pulsed dosing of vancomycin (14.3%, $P=0.02$) compared with a recurrence rate of 45% in patients on other regimens [40]. The data shows that tapered or pulsed dosing regimens of vancomycin leads to an apparent better cure of recurrent CDI.

Bacteriotherapy

Fecal microbiota transplantation (FMT) refers to the infusion of fecal suspension from a healthy donor with the aim of reinstating the gut microbiota of the recipient for curative purposes. The continuous use of antibiotics leads to the suppression of the host gut microbiota leading to a deficiency in microbes, which generally dominate within the gut microbiota and a decrease in the overall microbiome diversity [48]. Less diversity in colonic microbiota in patients with recurrent CDI compared to healthy individuals has also been demonstrated in some studies [49]. The resultant effect allows the overgrowth

of *C. difficile* and the production of toxins leading to CDI and recurrent CDI. Essentially, the role of fecal transplantation of stool from healthy individuals is to reestablish the diverse, "normal" gut microbiome within the colon breaking the cycle of recurrence.

Multiple studies support the safety and efficacy of FMT in the treatment of *C. difficile*-associated diarrhea in patients with recurrent disease after initial antibiotic therapy [50]. There is also mounting evidence in the efficacy of FMT in severe *C. difficile*- associated diarrhea [51]. The Food and Drug Administration has approved FMT as an investigational new drug for use in refractory or re-current CDI after failure of standard treatment regimens [52]. Surawicz *et al* recommend FMT in recurrent or relapsing CDI characterized by at least three episodes of mild-to-moderate CDI with lack of clinical response to a 6-8 week taper with vancomycin with or without an alternative antibiotic [19]. Additionally, Bakken *et al* have proposed the use of FMT in moderate CDI not responding to standard therapy (vancomycin) for at least a week and severe CDI with no response to standard therapy after 48 h [53] (Table 2).

Donor screening and selection

The majority of reported FMT procedures were performed with the instillation of fresh stool suspensions from related donors. The ideal route of administration is yet to be determined. Administration of fecal suspensions by gastroscopy, nasogastric tube, or nasojejunal tube were marginally less effective than other routes of administration such as rectal tube/enema, or colonoscopy in a conducted systematic review. Colonoscopic FMT has a slightly higher cure rate than nasogastric FMT [54].

Donor screening protocols are essential to minimize the risk of transmitted infection. Screening of donors include full blood count, liver function tests, screening for hepatitis A, B and C, human immunodeficiency virus I and II, human T-cell lymphotropic virus, Cytomegalovirus, Epstein-Barr virus, syphilis, stool tests for *C. difficile* toxin A and B, stool microscopy for ova cysts and parasites and selective stool culture (e.g., for *Salmonella*, *Shigella*, *Escherichia coli* O157:H7 and *Yersinia*) [55]. In addition to lab testing, a medical history is taken to exclude people with high risk sexual behaviors, use of antibiotics within the preceding 3 months, history of gastrointestinal comorbidities such as irritable bowel syndrome, inflammatory bowel disease, and chronic diarrhea [53].

Historically, donors have been family members, intimate partners, however, Hamilton *et al* demonstrated that there

Table 2 Proposed indications for fecal microbiota transplantation [19,52]

Three or more episodes of recurrent mild to moderate CDI with failure to respond to a 6-8 week taper with vancomycin with the inclusion or exclusion of an alternative antibiotic
Moderate CDI with no clinical response to standard therapy for at least 1 week
Two or more episodes of severe CDI requiring hospitalization
Severe CDI with no response to standard therapy after 48 h

CDI, *Clostridium difficile* infection

were no significant differences in infection clearance for fresh versus frozen samples, or inpatient identified donors versus standardized donors (using banked frozen fecal material) [56]. Youngster *et al* also demonstrated the use of oral frozen encapsulated fecal capsules from unrelated donors in the treatment of recurrent CDI, with a significant clinical resolution of diarrhea of 90% [57]. The use of oral capsules will streamline the procedure, making it accessible to a larger population. A number of nonprofit organizations are currently providing ready to use frozen fecal microbiota preparations with large scale production in the pipeline [58]. Fuentes *et al* showed that FMT enabled a therapeutic reset from a diseased state towards a healthy profile by analyzing the microbiota of patients before and after FMT [59]. This use of metagenomic and metatranscriptomic analyses of human gut microbiota could contribute to the development of biomarkers that can predict recurrent CDI and therapeutic outcomes which could potentially lead to improved outcomes in CDI [60].

Other antibiotics

Rifaximin: Mattila *et al* retrospectively evaluated the efficacy of using rifaximin in the treatment of patients with recurrent CDI. After 12 weeks of therapy 17 of 35 patients (53%) had no relapse. Rifaximin can be considered as an optional treatment for recurrent CDI [61].

Nitazoxanide: Nitazoxanide has been compared with vancomycin for treatment of CDI in a prospective randomized double-blinded control trial. There was a favorable initial response rate in 17 (77%) of 22 patients treated with nitazoxanide compared with 20 (74%) of 27 patients treated with vancomycin (95% CI, -24% to +28%). Evidently response rates were 94% (17 of 18 patients) in the nitazoxanide group and 87% (20 of 23 patients) in the vancomycin group in patients who completed therapy [62].

Probiotics

Probiotics contain a single culture or mixed culture of live microorganisms such as bacteria or yeast that can provide enormous health benefits. Mechanism of action of probiotics include direct activity against *C. difficile* via inhibition of adherence, modulation of the host response and stimulation of specific IgA antitoxin production [63-65]. Some probiotics available include the bacteria species *Lactobacillus* or *bifidobacteria*, which are part of the normal gastrointestinal microbiota and *Saccharomyces boulardii* a yeast (fungal) probiotic agent [66,67].

Administration of *lactobacilli* and *bifidobacteria* to prevent antibiotic-associated diarrhea and *C. difficile* diarrhea in older inpatients (PLACIDE trial involving 2941 older adults with antibiotic exposure) did not reduce CDI risk (RR 0.71; 95% CI 0.34-1.47; P=0.35) [68]. A Cochrane review in 2008 on the use of probiotics for the treatment of CDI concluded that there was insufficient evidence to recommend probiotics as an adjunct to antimicrobial therapy for treatment of CDI, however probiotics

may be useful for treatment of non-severe CDI, particularly in the setting of recurrent disease [69,70].

Anion-binding resins

The use of anion-binding resins as a possible alternative to antimicrobial therapy is an evolving area. CDI is a toxin-mediated disease, and thus neutralizing the toxins would seem to be an effective way of treating it without altering bowel flora. The anion-binding resins colestipol and cholestyramine have not been found to be effective in primary therapy for CDI, however, they are beneficial as adjunctive therapy for relapsing infection [71]. Tolevamer is a non-absorbable anionic polymer that sequesters toxin A and toxin B [72]. Louie *et al* showed that tolevamer was associated with a lower recurrence rate of CDI compared to vancomycin, however it was noninferior to vancomycin in regards to time to resolution of diarrhea (P=.02) [73].

Immunoglobulins and vaccines

The presence of levels of anti-toxin antibodies in higher amounts, is associated with a lower disease duration and declining recurrence rates. Immunoglobulins to anti-toxin A are thought to play the biggest protective role [41,74]. The efficacy of two neutralizing, human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1), was evaluated in a randomized, double-blind placebo controlled study among 200 patients (101 in the antibody group and 99 in the placebo group); the results showed a significant lower rate of recurrence of CDI in the subset of patients treated with monoclonal antibodies compared to placebo (7% vs. 25%; P<0.001) [75].

Preliminary results on the use of a parenteral vaccine against toxins A and B have also been excellent. The *C. difficile* toxoid vaccine induced immune responses to toxins A and B in patients with recurrent CDI who were on nearly continuous treatment with oral vancomycin to treat recurrent episodes of CDI. All the 3 patients were able to discontinue treatment with oral vancomycin without any recurrence of CDI [76]. These results are promising, a *C. difficile* toxoid vaccine could potentially be used to control CDI.

Nontoxicogenic *C. difficile* (NTCD) strain

There are strains of *C. difficile* that do not produce toxins due to the absence of genes for toxin production. These strains are referred to as NTCD strains. NTCD strains can also colonize hospitalized patients and be found in the hospital environment. By and large colonized patients are usually asymptomatic. Recent phase 2 trial among 173 patients who were diagnosed as having CDI (first episode or first recurrence) and had recovered following treatment with metronidazole or vancomycin, demonstrated the safety and efficacy of NTCD-M3 spores in colonizing and preventing recurrent CDI [77]. The theoretical likelihood that NTCD could acquire

toxin genes through horizontal gene transfer from toxigenic strains of *C. difficile* has been a concern given its occurrence in *in vitro* experiments [78].

Emerging therapies

CRS3123 is a favorable therapeutic agent that selectively inhibits the growth, spore and toxin production of *C. difficile*. The use of oral CRS3123 in hamsters resulted in a long lasting efficacy with essentially no recurrence, in significant contrast to existing CDI therapy with vancomycin [79]. CRS3123 has not demonstrated any cross-resistance to existing antibiotics and remains active against all tested *C. difficile* strains, more importantly the epidemic fluoroquinolone-resistant NAP1/BI/027 strain. Currently, CRS3123 is entering the clinical phase of development with promising therapeutic effects for the treatment of CDI [80].

Cadazolid, an oxazolidinone antibiotic, has demonstrated its potency *in vitro* against *C. difficile*, in addition to the epidemic BI/NAP1/027 strain [79]. A recent phase 2 multicenter, randomized, double-blinded study (NCT01222702; EUDRACT 2010-020941-29) assessed the efficacy and safety of oral cadazolid in treatment of CDI. A superior continual clinical response rate was noted with cadazolid (46.7-41 60.0%) compared with vancomycin (33.3%) [81].

Surgical management of *C. difficile*

Early surgical consultation should be considered in all patients with severe or fulminant CDI. Increasing consensus suggests that early surgical intervention is appropriate in the setting of peritoneal signs, severe ileus, toxic megacolon, and multi-organ failure [82]. Subtotal colectomy which involves the removal of the colon, with the rectum remaining *in situ* with an end ileostomy is currently the recommended surgical procedure of choice for fulminant CDI with closure of the ileostomy and ileo-rectal anastomosis after colonic inflammation resolves [83]. An alternative surgical approach to colectomy is the creation of diverting loop ileostomy and colonic lavage. This surgical procedure involves creating a loop ileostomy, with intraoperative colonic infusion and lavage with warmed polyethylene glycol solution via the ileostomy, and postoperative instillation of vancomycin flushes antegradely via the ileostomy [84]. A case-controlled study at the University of Pittsburgh showed a reduced mortality in patients who had undergone a loop ileostomy with colonic lavage, in comparison with historical controls who had undergone a colectomy (19 vs. 50%; odds ratio 0.24; P=0.006). Preservation of the colon was achieved in 39 of 42 patients (93%) [85].

Concluding remarks

Although the efficacy of metronidazole is declining, it remains the initial therapy for the majority of patients who

have mild-to-moderate infection, and as the treatment of choice for the first recurrent episode of CDI. Vancomycin continues to be recommended as initial therapy for severe CDI. Early surgical consultation is required in the event of severe complicated CDI.

The treatment of multiple recurrences of CDI is challenging. The use of FMT presents an enormous breakthrough as a therapy for recurrent CDI, however multicenter RCTs with long-term follow up are essential to assess the efficacy and safety of FMT.

There are many novel treatment strategies emerging involving the use of non-antibiotics, which appear promising. They provide optimistic approaches to future therapy. However, there is limited knowledge about the safety and efficacy of these treatments. Further research should be conducted to enable these treatment modalities to be widely accepted.

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