Clostridium difficile infection: management strategies for a difficult disease

Ther Adv Gastroenterol
2014, Vol. 7(2) 72–86
DOI: 10.1177/1756283X13508519

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Abstract: *Clostridium difficile* was first described as a cause of diarrhea in 1978 and in the last three decades has reached an epidemic state with increasing incidence and severity in both healthcare and community settings. There also has been a rise in severe outcomes from *C. difficile* infection (CDI). There have been tremendous advancements in the field of CDI with the identification of newer risk factors, recognition of CDI in populations previously thought not at risk and development of better diagnostic modalities. Several treatment options are available for CDI apart from metronidazole and vancomycin, and include new drugs such as fidaxomicin and other options such as fecal microbiota transplantation. This review discusses the epidemiology, risk factors and outcomes from CDI, and focuses primarily on existing and evolving treatment modalities.

Keywords: *Clostridium difficile* infection, risk factors, management, recurrent infection, severe infection

Introduction

Clostridium difficile is a Gram-positive spore forming bacterium, first isolated in 1935 and first described as a cause of diarrhea in 1978 in a patient with pseudomembranous colitis [Bartlett *et al.* 1978]. In the past three decades, *C. difficile* has reached an epidemic state with increasing incidence and severity in both healthcare and community settings [Khanna *et al.* 2010, 2012b]. *C. difficile* infection (CDI) is now among the most common causes of hospital-acquired infection along with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*, and is the commonest cause of infectious diarrhea in hospitals and long-term care settings [Miller *et al.* 2011]. Over the past two decades, newer risk factors for CDI have emerged, and more recently a new hypervirulent strain of *C. difficile* has been described which may explain this increase. There have been several advances with the development of newer diagnostic modalities and treatment options such as new drugs and fecal microbiota transplantation (FMT) [Khanna *et al.* 2012b; Kelly, 2013]. Despite advances in both drug treatment and infection control practices, there continues to be an increase in the rates complications from CDI such as severe and severe-complicated infection, treatment failure and recurrence rates which are associated with increasing mortality and healthcare costs [Kelly and Lamont, 2008; Khanna *et al.* 2012b]. This review will discuss the epidemiology, risk factors, and outcomes from CDI and focus primarily on management strategies for CDI.

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Epidemiology and risk factors

In the past two decades, epidemiological data derived from US national administrative databases, hospital-based reports and population-based studies have shown a two to four fold increase in the incidence of CDI in the past two decades, especially in the elderly [Ricciardi *et al.* 2007; Zilberberg *et al.* 2008a, 2008b;[Muto *et al.* 2005; McDonald *et al.* 2006]. An outbreak in Quebec reported in 2004 showed increasing severity and a high mortality rate of 6.9% [Pepin *et al.* 2004].

There have been relatively few studies describing the epidemiology of community-acquired CDI [Allard *et al.* 2011; Kuntz *et al.* 2011; Khanna *et al.* 2012c, 2012g; Chitnis *et al.* 2013]. A population-based study from Olmsted County, MN, showed that the incidence of both community-acquired increased by 5.3 fold from 1991 to 2005,

and a large proportion of cases (41%) were community-acquired [Khanna *et al.* 2012g]. Studies in the pediatric population have shown that the incidence in children has increased up to 12.5-fold in the last two decades [Khanna *et al.* 2013b; Kim *et al.* 2008]. Adult patients with community-acquired CDI are younger, have fewer comorbidities and less frequently have severe disease than patients with hospital-acquired infection [Khanna *et al.* 2012g]. Hence, CDI is now commonly being identified in populations that were previously considered to be low-risk such as children and community dwellers who lack traditional risk factors for CDI [Khanna *et al.* 2012f; Chitnis *et al.* 2013; Lessa, 2013].

The traditional risk factors for CDI include age >65 years, recent hospitalization, increased length of hospital stay, long-term healthcare facility residence, antibiotic exposure, and comorbidities such as malignancies, chronic kidney disease, inflammatory bowel disease and immunosuppression [Khanna and Pardi, 2010; Khanna *et al.* 2012b, 2012e]. Additional risk factors include contact with active carriers, consumption of contaminated food products such as processed meats, hypoalbuminemia, use of proton-pump inhibitors (PPIs), gastrointestinal endoscopic procedures and enteral tube feeding. There is often a lack of traditional risk factors in patients with community-acquired CDI, such as antibiotic exposure, older age and recent hospitalization, which suggests alternate novel risk factors for CDI and newer modes of transmission of CDI in the community. Studies have shown that patients with community-acquired CDI are likely to have a recent healthcare exposure other than hospitalization, with up to 94% of patients having had a recent outpatient or emergency room visit, thus suggesting that a short duration of healthcare exposure without hospitalization may also be a risk factor for CDI [CDC, 2012; Chitnis *et al.* 2013; Khanna *et al.* 2013b; Lessa, 2013].

Potential risk factors explaining an increase in the incidence of community-acquired CDI include contaminated food consumption, person-to-person, environment-to-person and potentially animal-to-person spread. *C. difficile* strains that cause human disease have been identified in retail meat and meat products including beef, chicken and pork [Jhung *et al.* 2008; Weese *et al.* 2010]. Person-to-person spread is important both in hospitals and outside the hospitals. Recent practice guidelines have suggested that visitors to hospital rooms harboring patients with CDI should practice the same isolation precautions as healthcare personnel [Surawicz *et al.* 2013]. Exposure to infants and children who may be asymptomatically colonized with *C. difficile* may be a risk factor for recurrent CDI in mothers in the postnatal period. Another potential mechanism for acquisition of CDI in the community is exposure to colonized or infected persons, such as healthcare workers, and studies have shown that family members of patients with recent infection have a higher risk of CDI [Otten *et al.* 2010].

Risk factors for adverse outcomes

Adverse outcomes from CDI include severe and severe-complicated infection, treatment failure and recurrent infection. According to guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), severe CDI is defined as peripheral white cell count ≥15,000 cells/μl or an increase in serum creatinine ≥1.5 times above baseline [Cohen *et al.* 2010]. Severe-complicated infection is defined by: hypotension, shock and sepsis, which may require intensive care unit level of care; ileus, megacolon and perforation, which may necessitate colectomy; or death secondary to CDI [Cohen *et al.* 2010]. Studies have assessed additional predictors of severe and severe-complicated CDI,[Lungulescu *et al.* 2011; Shivashankar *et al.* 2013], which include increasing age, concomitant antibiotic and antimotility medication use, hypoalbuminemia, more severe diarrhea, acute kidney injury, comorbidities such as chronic kidney disease, presence of fever and presence of pseudomembranes or megacolon [Belmares *et al.* 2007; Zar *et al.* 2007; Fujitani *et al.* 2011; Keddis *et al.* 2012; Khanna *et al.* 2013c]. It is important to identify patients with severe or severe-complicated infection, as treatment recommendations are based on disease severity [Cohen *et al.* 2010]. Gastric acid suppression medications, such as PPIs, have been implicated as a risk factor for CDI [Khanna *et al.* 2012d], but use of these medications has not been associated with severe CDI or treatment failure in patients with CDI [Khanna *et al.* 2012a]. The data on the risk of recurrent CDI with gastric acid suppression are controversial [Kim *et al.* 2010, Khanna *et al.* 2012a]. A study has shown that prior appendectomy decreases the risk of primary CDI [Merchant *et al.* 2012a] and there is conflicting evidence on whether appendectomy increases the risk of recurrent CDI [Fujii *et al.* 2010; Im *et al.* 2011].

Subgroup analysis from a large population-based study showed that adult patients with CDI who had undergone prior appendectomy had no differences in treatment failure, development of severe or severe-complicated CDI and recurrence rates compared with patients without appendectomy [Khanna *et al.* 2013a]. Therefore, with the current data, prior appendectomy should not be a consideration in medical decision making for the diagnosis or management of CDI.

Clinical diagnosis

The clinical diagnosis of CDI requires an appropriate clinical presentation, which includes watery diarrhea (defined as ≥3 loose stools in 24 hours) with or without abdominal pain, fever or ileus [Cohen *et al.* 2010; Surawicz *et al.* 2013]. This should be supplemented by a positive laboratory test for *C. difficile* or the endoscopic presence of pseudomembranes, which are highly suggestive of CDI. The laboratory findings should be interpreted in the context that different stool tests have different sensitivities and specificities for the diagnosis of CDI.

Fecal leucocyte testing is not sensitive for CDI and stool may be positive for fecal leukocytes in less than 30% of patients with CDI [Marx *et al.* 1993; Reddymasu *et al.* 2006]. Stool culture is the most sensitive test and hence considered the gold standard for detecting *C. difficile*, but is limited by its slow turnaround time. Although enzyme immunoassay (EIA) to detect toxins A and B produced by *C. difficile* is a rapid test, it lacks sensitivity. EIA for glutamate dehydrogenase enzyme is very sensitive but not very specific and is being adopted by some laboratories as a screening test in combination with another more specific confirmatory test [Carroll, 2011]. Polymerase chain reaction (PCR) used to detect genes *tcdB*, which encodes the toxin and/or *tcdC*, which negatively regulates the toxin produced by *C. difficile* is considered an alternative gold standard to stool culture with studies demonstrating excellent sensitivity, specificity and test-retest reliability [Sloan *et al.* 2008; Khanna *et al.* 2012h]. The PCR test has a fast turnaround time and due to this it is being more widely adapted across different laboratories in place of toxin EIA [Carroll, 2011].

The yield of repeat PCR testing for *C. difficile* is low. In a study evaluating over 15,000 stool PCR tests for *C. difficile*, repeat testing within 2 weeks of an initial test was uncommon and happened in less than 13% of all tests. Increased age, male sex and inpatient location were predictors of repeat testing. After an initial negative test, the percentage of patients having a subsequent positive test was very low (2.7% in 7 days and 3.2% in 14 days) [Khanna *et al.* 2012h].

It is of utmost importance that stool testing for *C. difficile* be performed only in patients who exhibit signs and symptoms of CDI. Patients who are colonized with *C. difficile* and do not exhibit symptoms should not be tested. Treating asymptomatic patients with medications for CDI may potentially disrupt gut microflora and it is not recommended to eradicate colonization in these patients due to lack of any perceived benefit.

Gastric acid suppression and CDI

The role of gastric acid in the pathogenesis of CDI is controversial. Recent data have suggested that circumventing the potential protective effect of gastric acid by PPIs or histamine-2 (H2) receptor blockers may be a risk factor for the acquisition of CDI [Dial *et al.* 2005, 2006]. However, there is conflicting evidence as to whether acid does or does not kill *C. difficile* spores [Wilson *et al.* 1985; Rao *et al.* 2006]. Furthermore, studies have found that after controlling for important confounders, the use of PPI and H2 blockers have not been associated with the risk of CDI [Pepin *et al.* 2005b] or adverse outcomes from CDI [Khanna *et al.* 2012a]. Thus, it is not clear if acid suppressing drugs are independent risk factors for CDI [Khanna *et al.* 2012d], although the US Food and Drug Administration (FDA) has recently issued a warning that PPI are associated with an increased risk of CDI. Three retrospective studies suggested an increased risk of recurrent CDI in patients on PPIs [Cadle *et al.* 2007; Kim *et al.* 2010; Linsky *et al.* 2010], although a subgroup analysis of a large randomized controlled trial did not demonstrate a difference in the rates of recurrent CDI in patients with or without exposure to PPI and H2-receptor antagonists [Linsky *et al.* 2011].

In a population-based study, patients taking acid suppressive medications were more likely to have severe (34.2% *versus* 23.6%, $p = 0.03$) or severe-complicated CDI (4.4% *versus* 2.6%, $p = 0.006$) than patients not on acid suppression on univariate analysis. However, patients on acid suppression medications were significantly older and had more comorbid conditions, and on multivariate

analysis after controlling for comorbidities and age, acid suppression medication use was not associated with severe or severe-complicated CDI. In addition, there was no relationship between acid suppression and treatment failure or recurrent CDI [Khanna *et al.* 2012a]. Therefore, in CDI patients who have an absolute indication for gastric acid suppression medications, these agents may be continued during treatment of CDI. However, consideration may be made to stop these medications if there is no absolute indication for their use.

Management of CDI

General measures

Supportive care is an essential component of therapy for CDI. As for any diarrheal illness, initial therapy includes careful management of fluid and electrolyte balance. After initial stabilization, data must be obtained to categorize severity and history of prior CDI episodes must be obtained as therapy depends on these parameters. Antimotility agents, such as narcotics and loperamide, should be stopped as these are associated with adverse outcomes [Shivashankar *et al.* 2013]. Studies have suggested that the use of concomitant systemic antibiotics is associated with a decreased cure rate and an increased risk of recurrent CDI [Garey *et al.* 2008; Mullane *et al.* 2011]. Therefore, concomitant systemic antibiotics should ideally be discontinued if possible, and if ongoing antibiotic therapy is absolutely needed, targeted narrow spectrum agents should be used for the shortest duration possible. These decisions may be guided by culture and sensitivities for the systemic infection to choose the appropriate systemic antibiotics. In elderly and severely ill patients, with a high clinical suspicion of CDI, empiric antibiotic treatment for CDI may be started when the diagnosis is suspected due to risk factors and symptoms but the results of stool tests are pending [Surawicz *et al.* 2013].

Measures for infection control include placing patients in isolation with contact precautions, including the use of gloves and gowns, hand washing with soap and water, and the use of chlorine-containing agents for disinfection [Kelly and Lamont, 2008; Orenstein *et al.* 2011]. Daily cleaning of hospital rooms with germicidal bleach wipes in wards with a high incidence of hospital-acquired CDI reduces infection rates and prolongs the time between hospital-acquired CDI cases [Orenstein *et al.* 2011]. Detailed guidelines for infection prevention for CDI have been published by SHEA and IDSA [Dubberke *et al.* 2008; Cohen *et al.* 2010].

Metronidazole, vancomycin and fidaxomicin

According to the IDSA/SHEA guidelines, patients with the first infection or first recurrent episode of mild to moderate CDI should be treated with metronidazole in the absence of contraindications [Cohen *et al.* 2010]. Randomized controlled trials comparing vancomycin and metronidazole for treatment of CDI demonstrated cure rates of over 90% and there were no differences in differences when metronidazole was compared to vancomycin [Teasley *et al.* 1983; Wenisch *et al.* 1996]. The treatments in these trials were not stratified by disease severity. Metronidazole is an inexpensive, effective treatment but its use for CDI is not approved by the FDA. In mild-to-moderate CDI, oral metronidazole (e.g. 250–500 mg 3–4 times a day for 10–14 days) is considered equivalent to vancomycin [Zar *et al.* 2007; Cohen *et al.* 2010; Surawicz *et al.* 2013].

CDI may be more refractory to metronidazole treatment than in the past [Pepin *et al.* 2005a]. In one study, from 1991–2002, the rate of metronidazole failure was 9.6%, but during an outbreak in 2003–2004, that rose to almost 26% [Pepin *et al.* 2005a], a rate close to that reported from Houston where 22% of patients treated with metronidazole had continued symptoms after 10 days or more of therapy [Musher *et al.* 2005]. Lack of response to initial therapy with metronidazole has been associated with increased mortality [Musher *et al.* 2005]. However, at this time there are no models in patients with mild to moderate CDI to predict metronidazole failure. After adjusting for appropriate confounders, metronidazole may be associated with more complications than vancomycin [Pepin *et al.* 2004], has more side effects (including nausea, disulfiram-like reaction if drinking alcohol, metallic taste and peripheral neuropathy), and is not recommended for children or during lactation or pregnancy. Patients who do not improve promptly (within 72–96 hours) should be reassessed for alternative causes of diarrhea. If other pathologies have been ruled out, metronidazole should be switched to vancomycin [Cohen *et al.* 2010]. Despite these concerns, owing to the cost of vancomycin and theoretical concerns about the development of vancomycin resistance

enterococci, metronidazole is still suggested as the first-line therapy in mild to moderate cases.

Vancomycin is a reliable but more expensive treatment and was the first drug approved by the FDA for the management of CDI. According to the IDSA/SHEA guidelines, oral vancomycin is recommended for the treatment of severe CDI and, in combination with metronidazole, for severe-complicated infection [Cohen *et al.* 2010; Surawicz *et al.* 2013]. Although response rates are similar to metronidazole in mild to moderate disease, vancomycin is the preferred treatment in severely ill patients due to superior cure rates in these patients (97% *versus* 76%), although subsequent relapse rates were not significantly different between these two treatments [Zar *et al.* 2007].

Since oral vancomycin is poorly absorbed, high stool concentration can be achieved without systemic side effects. The recommended dose is vancomycin 125 mg 4 times a day for 10 days. A higher dose (250–500 mg) is recommended for seriously ill patients with severe-complicated CDI, along with intravenous metronidazole, and vancomycin enemas if an ileus is present [Cohen *et al.* 2010]. Patients who do not improve promptly should be reassessed, since failure of vancomycin therapy is quite unusual and additional therapy, including surgery, may be indicated.

An interesting recent study assessed the effect of ongoing infection compared with persistent intestinal inflammation by measuring fecal cytokine levels and fecal *C. difficile* burden, and assessed CDI outcomes. Bacterial burden at the time of diagnosis or the rate of decrease of burden did not correlate with clinical measures or outcomes. There was no significant difference in the microbiologic response of *C. difficile* to metronidazole *versus* vancomycin. Elevated fecal inflammatory makers such fecal CXCL-5 messenger RNA (mRNA), interleukin-8 (IL-8) mRNA and IL-8 protein at the time of CDI diagnosis, were associated with poor outcomes and remained elevated in those with persistent disease, suggesting that the response to therapy may be related to intestinal inflammation [El Feghaly *et al.* 2013].

Fidaxomicin is a macrocyclic antimicrobial agent with little or no systemic absorption after oral administration and narrow spectrum against Gram-positive aerobic and anaerobic bacteria, including *C. difficile* [Gerber and Ackermann, 2008]. *In vitro* studies showed that fidaxomicin was more active than vancomycin against *C. difficile* [Ackermann *et al.* 2004; Finegold *et al.* 2004; Karlowsky *et al.* 2008].

In multicenter, randomized, double-blind phase III clinical trials, patients with CDI were randomized to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg 4 times daily) orally for 10 days [Louie *et al.* 2011; Cornely *et al.* 2012]. In one study, the rate of clinical cure with fidaxomicin was similar to vancomycin (88.2% *versus* 85.8%, respectively), but fewer patients in the fidaxomicin group had a recurrence (15.4% *versus* 25.3%, $p = 0.005$) [Louie *et al.* 2011]. Interestingly, on subgroup analyses, the rates of recurrence were significantly lower with fidaxomicin (7.8%) than with vancomycin (25.5%) among patients with the nonhypervirulent strain of *C. difficile*. In the other trial, fidaxomicin was also noninferior to vancomycin for achieving clinical cure and superior to prevent recurrence [Cornely *et al.* 2012]. Subsequent post hoc analyses of these trials showed that, when patients received systemic antibiotics concurrent with CDI treatment, the cure rate was significantly higher for fidaxomicin compared to vancomycin (90% *versus* 79.4%; $p = 0.04$), and recurrence rates were lower for fidaxomicin (16.9% *versus* 29.2%; $p = 0.048$) [Mullane *et al.* 2011]. Therefore, fidaxomicin may have a favorable profile compared with oral vancomycin when patients require ongoing concomitant systemic antibiotics.

There are no randomized data comparing fidaxomicin with metronidazole for a first episode of mild to moderate CDI, for which metronidazole remains the initial treatment of choice. In addition, fidaxomicin has not been studied for efficacy in multiply recurrent CDI. Anecdotal experience from small case series has shown that fidaxomicin may be an option in patients with recurrent CDI [Orenstein, 2012; Johnson and Gerding, 2013]. Factors associated with recurrence include increasing age, severe CDI, concomitant antibiotic use, decreased anti-toxin A immunoglobulin G (IgG) levels and history of prior CDI [Hu *et al.* 2009; Johnson, 2009].

There are several pharmacoeconomic considerations for the use of fidaxomicin. The current average wholesale price for fidaxomicin is US$135 for each 200 mg dose compared with US$0.72 for 500 mg dose of metronidazole, and US$31.81 for a 125 mg capsule of oral vancomycin [Lancaster

and Matthews, 2012]. Using the intravenous vancomycin solution orally costs significantly less than oral vancomycin capsules. With these considerations, fidaxomicin might be indicated for patients with an initial episode of CDI who are at a very high risk for subsequent recurrences and are infected with the nonhypervirulent strain, or in patients who have a severe intolerance or allergic reaction to oral vancomycin, although this has not been subjected to rigorous study, and a recent analysis that assumed that if approximately 50% of CDI due to the hypervirulent strain, a course of fidaxomicin would need to cost ≤US$150 to be cost-effective in the treatment of all CDI cases and between US$160 and US$400 to be cost-effective for those with a nonhypervirulent strain (i.e. treatment based on strain typing) [Bartsch *et al.* 2013]. Contrary to this study, another economic model suggested that fidaxomicin may be cost-effective in patients receiving concomitant systemic antimicrobials in patients with mild to moderate CDI. Fidaxomicin was dominated by oral vancomycin if CDI was caused by the hypervirulent strain and was dominant in institutions that did not compound liquid oral vancomycin [Stranges *et al.* 2013].

To summarize, patients with the first episode or first recurrence of mild to moderate CDI should be treated with metronidazole. For severe disease, as defined by leukocytosis or renal dysfunction, and for second or additional recurrences, vancomycin should be the treatment of choice. For patients with severe-complicated CDI, intravenous metronidazole supplemented by high dose vancomycin is recommended, with close clinical follow up to assess response. In patients who cannot take oral medications (e.g. ileus), vancomycin should be administered *via* nasogastric tube and/or enema [Cohen *et al.* 2010]. In rare instances, where patients have a primary treatment failure to more than one medication regimens, FMT may be an alternative management strategy.

Prolonged vancomycin treatment regimens

If the initial episode was treated with vancomycin, a tapered and pulsed regimen or just a pulsed regimen of vancomycin may be considered; none of these recommendations for extended vancomycin regimens have been studied in randomized controlled trials. In a small study, 22 patients with recurrent CDI underwent a tapering dose of oral vancomycin for 21 days and a pulse dose of vancomycin for 21 days and had no recurrences in a mean follow up of 6 months (range 2-12 months) [Tedesco *et al.* 1985].

Data analyzed from a clinical trial of a probiotic adjunct to antibiotic therapy in patients who had one or more CDI recurrences demonstrated that longer, tapered, pulsed vancomycin dosing were more effective than conventional regimens. Patients who received a standard 10–14 day course had higher recurrence rates of up to 54% compared with 31% in those who had tapering regimens (gradually lowered doses) and 14% in those who had pulsed (every 2–3 day) regimens [McFarland *et al.* 2002].

Other medication regimens

Additional treatment options for CDI include rifaximin, nitazoxanide, intravenous immunoglobulin (IVIG), monoclonal antibodies, vaccines and probiotics. Rifaximin is a broad spectrum antimicrobial agent selective to the gastrointestinal tract, which has activity against most Gram-negative and Gram-positive bacteria, as well as anaerobes and aerobes and excellent *in vitro* activity against *C. difficile* [Koo and Dupont, 2010]. Rifaximin is not considered to cause significant alterations to the gut microbiota [Dupont *et al.* 2005]. It has been shown to be effective for the treatment of CDI in smaller clinical studies and case reports [Berman, 2007; Johnson *et al.* 2007; Rubin *et al.* 2011]. A recent randomized controlled trial demonstrated that rifaximin was effective against CDI but did not meet the noninferiority definition compared to vancomycin (57% for rifaximin *versus* 64% for vancomycin) to attain a clinical success (absence of fever, abdominal pain or diarrhea) and was similar to vancomycin for resolution of diarrhea and rates of recurrence [Pardi *et al.* 2012]. Rifaximin is currently not recommended as a monotherapy for CDI, but may be used for recurrent CDI following treatment with oral vancomycin (125 mg orally 4 times a day for 14 days) in the form of a 'rifaximin chaser (400 mg orally twice daily for 14 days)' [Kelly and Lamont, 2008; Garey *et al.* 2011].

Nitazoxanide is an antiparasitic drug that is also active against *C. difficile*, and has been shown to be as effective as vancomycin and metronidazole for the treatment of CDI [Musher *et al.* 2007, 2009]. Nitazoxanide has not been compared with other drugs, and there is a lack of long-term safety and efficacy data. It may be considered as an

alternate therapy in those patients with multiple recurrences despite multiple courses of vancomycin and metronidazole, who may not be candidates for fecal transplant.

IVIG has been used to treat recurrent CDI with variable success. There are no randomized controlled trials showing a benefit of IVIG for CDI [Abougergi *et al.* 2010]. It is believed that the mechanism of action for IVIG may include the presence of antibodies against *C. difficile* toxin A and toxin B [Leav *et al.* 2010; Abougergi and Kwon, 2011]. In a large, randomized, controlled study of monoclonal antibodies against *C. difficile* toxins A and B in addition to antibiotic therapy, the rate of CDI recurrence was lower among patients treated with monoclonal antibodies (7% *versus* 25%; $p < 0.001$) [Lowy *et al.* 2010]. A phase III study is underway to further establish the safety and efficacy of monoclonal antibody treatment for CDI.

Probiotics in CDI

There is limited evidence for the use of concomitant probiotics for treatment of CDI or for prevention of recurrent CDI. *Saccharomyces boulardii* has been studied in several clinical trials in combination with oral therapies for CDI and has been associated with decreased CDI recurrences in those with recurrent CDI [Surawicz *et al.* 1989, 2000; McFarland *et al.* 1994]. A randomized controlled trial of *Lactobacillus rhamnosus* did not show efficacy in treatment of recurrent CDI [Wullt *et al.* 2003].

A recent meta-analysis suggested that there is strong evidence from numerous large trials for efficacy in prevention of antibiotic-associated diarrhea for *S. boulardii*; the evidence for efficacy of of *S. boulardii* in the treatment of *C. difficile* is weak [McFarland, 2010]. A Cochrane analysis concluded that there was lack of sufficient evidence to recommend probiotics, as an adjunct to antibiotics in the treatment of CDI [Pillai and Nelson, 2008]. Therefore, there are no strong data to support the use of concomitant probiotics for the treatment of CDI. There are no data to support the use of probiotics in the treatment of severe CDI.

In a large meta-analysis of 20 trials including 3818 patients, probiotics reduced the incidence of CDI by 66% [pooled relative risk (RR), 0.34; 95% confidence interval (CI), 0.24–0.49]. The number needed to treat was calculated assuming a 5% incidence of antibiotic-associated CDI, and probiotic prophylaxis would prevent 33 episodes (CI, 25–38 episodes) per 1000 persons treated with antibiotics [Johnston *et al.* 2012]. On the contrary, a large randomized controlled trial, with over 1400 patients in each group, which compared Lactobacilli and Bifidobacteria to placebo in the prevention of antibiotic-associated diarrhea and CDI in older inpatients, did not show any effect of probiotics in the reduction of CDI [Allen *et al.* 2013]. A nontoxigenic *C. difficile* strain VP20621 has been shown to achieve colonization in healthy patients and a phase II trial has been completed and final data are awaited [Villano *et al.* 2012]. Therefore, due to the lack of efficacy, concern for potential adverse events from probiotics and high cost, these agents are not recommended for the treatment of first episode of CDI, but may be considered to prevent recurrences in patients with recurrent CDI.

Fecal microbiota transplantation

Antibiotic usage disrupts the normal gut flora and leads to an increased predisposition to CDI. The risk of recurrent CDI after initial treatment of the first infection is approximately 20–25% [Kelly and Lamont, 2008; Khanna *et al.* 2012g] and is further increased up to 60% with the use of additional systemic antibiotics and subsequent CDI recurrences [Hu *et al.* 2009]. The pathophysiology of recurrent CDI involves ongoing disruption of the normal fecal flora and an inadequate host immune response. Standard CDI treatment with antibiotics such as metronidazole and vancomycin further disrupts colonic microbial communities that normally keep expansion of *C. difficile* populations in check. Since *C. difficile* spores are resistant to antibiotic therapy for CDI, they can germinate to vegetative forms after treatment has been discontinued and lead to recurrent CDI.

FMT is being used as an alternative to standard antibiotic therapy for recurrent CDI due to the ability to restore the colonic flora *via* infusion of a liquid suspension of intestinal microorganisms from the stool of a healthy donor. A randomized controlled trial compared an initial high dose vancomycin regimen (500 mg orally 4 times per day for 4 days) followed by FMT through a nasoduodenal tube to a full course of high dose vancomycin (500 mg orally 4 times per day for 14 days) or a high dose vancomycin regimen with bowel lavage alone. The primary endpoint was

the resolution of diarrhea associated with CDI without relapse after 10 weeks. Of 16 patients in the FMT group, 13 (81%) had resolution of CDI after the first infusion. The three remaining patients received a second infusion with feces from a different donor, with resolution in two patients (for an overall success rate of 94%). Resolution of CDI occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($p < 0.001$ for both comparisons with the FMT group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the FMT group on the infusion day [Van Nood *et al.* 2013].

A systematic review of 27 studies and case reports, including 317 patients with recurrent CDI treated with FMT, showed an overall success rate of 92%, with 89% of patients responding after a single treatment. In these studies, 35% of patients received FMT by enema, with a response rate of 95%, 23% by the nasogastric route, with a response rate of 76%, and 19% by colonoscopy, with a response rate of 89% [Gough *et al.* 2011].

Another study reporting FMT *via* colonoscopy in 43 patients with recurrent CDI included patients with underlying inflammatory bowel disease. The overall rate of infection clearance was 86% in response to a single infusion and there were no differences in outcomes relative to donor source and no serious adverse effects were reported [Hamilton *et al.* 2012]. Another recent study reported experience with FMT *via* colonoscopy for 70 patients with recurrent CDI. During the initial 12-week follow-up period, FMT resulted in the resolution of symptoms in all patients with nonhypervirulent *C. difficile* strain and in 89% of those infected with the hypervirulent strain [Mattila *et al.* 2012]. There have been no studies of FMT for prophylaxis in patients at a high risk of recurrence after a first episode of CDI, and there has been no head to head comparison of FMT with conventional CDI treatments.

Therefore, existing literature suggests that fecal transplant is safe and effective with over 500 cases of recurrent CDI with no serious adverse events reported to date. FMT appears to be an appropriate treatment option for multiple CDI recurrences and may be considered for refractory moderate to severe *C. difficile* diarrhea, failing standard therapy. The FDA had recently announced that an Investigational New Drug Application would be required for use of FMT for CDI, but this was later changed to the use of an informed consent process to ensure communication of potential risks. There are several considerations for FMT, which include donor selection (standard donor *versus* related donor), the need to screen donors for transmissible infectious diseases, standardization of stool preparation techniques, insurance reimbursement for donor testing, and long-term safety and efficacy of FMT in this population [Bakken *et al.* 2011]. Donor and recipient selection criteria for FMT in our practice are summarized in Table 1. These criteria are based on expert opinion and have not been prospectively validated [Bakken *et al.* 2011; Brandt, 2013; Brandt and Aroniadis, 2013]. The cost of FMT includes the cost of donor and recipient screening tests (Table 1), which are incurred by all methodologies, the cost of stool processing and the cost of endoscopic procedure for FMT. The costs associated with donor screening include: an office visit for history and physical examination, blood tests for acute and chronic hepatitis, human immunodeficiency virus (HIV) and syphilis; and stool tests for infections. The cost of preparation is variable and depends on the method and the apparatus used in the laboratory. The different routes of administration include nasogastric, nasoduodenal, enema and colonoscopic administration of fecal material. These costs are less than the cost of popular medication regimens for recurrent CDI and may be justified by data that show that the risk of long-term relapse free status after FMT is over 90% [Brandt *et al.* 2012].

Approach to severe and severe-complicated CDI

At the time of presentation, risk factors for development of severe and severe-complicated CDI must be ascertained. These include older age, presence of comorbidities and the concomitant use of certain medications such as immunosuppression, antibiotics, narcotics and antiperistaltic medications [Fujitani *et al.* 2011; Lungulescu *et al.* 2011; Shivashankar *et al.* 2013]. Other features include the presence of fever, severe abdominal pain and deranged laboratory parameters suggesting severe infection. These include and elevated white blood cell count ($\geq$15,000/µl), elevated creatinine ($\geq$1.5 times above baseline) and possibly low albumin [Cohen *et al.* 2010; Surawicz *et al.* 2013]. Patients with mild to moderate CDI

Table 1. Recipient and donor selection criteria and testing for fecal microbiota transplantation for *C. difficile* infection.

Recipient inclusion and screening	
Recipient inclusion criteria	• Multiple recurrent *C. difficile* infection proven by a positive *C. difficile* stool assay • Previous treatment with first-line therapies for *C. difficile* infection (vancomycin, metronidazole, or fidaxomicin) • Refractory moderate to severe *C. difficile* diarrhea, failing standard therapy after >1 week • Ability to stop concomitant systemic antibiotics • Able to safely undergo and consent to fecal transplant
Recipient exclusion criteria	• Severe immunosuppression
Laboratory testing for recipients	• HIV antibody • Syphilis enzyme immunoassay or RPR • Hepatitis A IgM • Hepatitis B surface antigen, hepatitis B surface and core antibody • Hepatitis C antibody
Donor inclusion and screening	
Donor inclusion criteria	• Healthy individuals with no exclusion criteria

Donor exclusion criteria	• Active communicable illness (HIV, HAV, HBV, HCV, etc.)
	• Metabolic syndrome
	• Autoimmune diseases
	• Recent acute diarrheal illness within 6 months
	• Chronic diarrheal disorder such as:
	  ○ Irritable bowel syndrome
	  ○ Inflammatory bowel disease
	  ○ Microscopic colitis
	  ○ Celiac disease
	• Known colonic malignancy
	• History of *C. difficile* infection
	• Hospitalization within the past 3 months
	• Antibiotic exposure within the past 3 months
	• Immunosuppressive or antineoplastic medication use
	• High risk sexual behavior (men having sex with men, multiple partners)
	• Illicit drug use, recent tattoos or incarceration
	• Exposure risk for hepatitis in past 12 months
	• Travel to high risk areas for infectious diarrhea in past 6 months
	• Neurological disease
	• Recent ingestion of allergen to which recipient is known to be allergic
	• Fever or any suspected infectious disease

Recommended laboratory testing for donors	• Human immunodeficiency virus antibody • Syphilis enzyme immunoassay or RPR • Hepatitis A IgM • Hepatitis B surface antigen, hepatitis B surface and core antibody • Hepatitis C antibody
Recommended stool studies for donors:	• Bacterial/enteric pathogen culture or PCR • *Clostridium difficile* stool assay • Ova and parasite exam • Cryptosporidial stool antigen • Microsporidia stool test

HIV, human immunodeficiency virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis A virus; IgM, immunoglobulin M; PCR, polymerase chain reaction; RPR, rapid plasma regain.

should be treated with metronidazole. Those with these laboratory markers of severity at presentation or who develop these markers during management of CDI should be treated with oral vancomycin instead of metronidazole [Zar *et al.* 2007]. If mild to moderate CDI evolves into severe CDI, treatment must be promptly changed from metronidazole to oral vancomycin. It may be reasonable to treat patients with prior episodes of severe CDI with oral vancomycin instead of

Table 2. Treatment options for recurrent *C. difficile* infection.

First recurrence:
Mild to moderate
Oral metronidazole 500 mg 3 times a day for 10–14 days
Mild to moderate CDI (no response to oral metronidazole / severe CDI previously)
Severe CDI
Oral vancomycin 125 mg 4 times a day for 10–14 days
Second recurrence:
Oral vancomycin tapered over 7 weeks
125 mg 4 times daily for 14 days
125 mg twice daily for 7 days
125 mg once daily for 7 days
125 mg once every other day for 8 days
125 mg once every third days for 15 days
Future recurrences
Fecal microbiota transplantation
Oral vancomycin 125 mg 4 times a day for 14 days, followed by rifaximin 400 mg twice daily for 14 days
Consider intravenous immunoglobulin, 400 mg/kg, repeated up to 3 times at 3-week intervals
Consider combination therapy with oral vancomycin and oral rifaximin

CDI, *Clostridium difficile* infection.

metronidazole even if their current episode does not meet the definition of severe infection. Additionally, patients with multiple risk factors for development of severe or severe-complicated CDI may be treated with oral vancomycin to prevent complications [Fujitani *et al.* 2011; Lungulescu *et al.* 2011; Shivashankar *et al.* 2013].

Clinical features defining severe-complicated CDI include admission to intensive care unit for CDI, presence of systemic inflammatory response syndrome (SIRS) criteria, hypotension with or without required use of vasopressors, ileus or megacolon, mental status changes, elevated serum lactate or presence of end-organ failure. These patients should be managed with a combination of high dose oral vancomycin (500 mg 4 times a day) and intravenous metronidazole. It is advisable to perform abdominal imaging and serial abdominal examinations to evaluate for the presence of megacolon in these patients. If there is ileus or megacolon, rectal infusion of vancomycin by retention enemas must be added to oral vancomycin and intravenous metronidazole. Early surgical consultation must be obtained on all patients with severe-complicated CDI. Surgical management may consist of total colectomy with end-ileostomy or diverting loop ileostomy and intracolonic lavage with polyethylene glycol followed by liquid vancomycin. Mortality rates from surgery for CDI are high and studies have shown that outcomes from early surgery are better than outcomes from delayed surgery. It has been shown that intraoperative colonic lavage with polyethylene glycol and postoperative colonic vancomycin flushes led to colon preservation in over 90% of patients and had significantly improved survival compared with historical controls who had undergone colectomy [Neal *et al.* 2011; Tsiouris *et al.* 2012].

Approach to recurrent CDI

The management of recurrent CDI remains a major challenge due to a paucity of clinical trials and hence evidence-based management guidelines. Recurrent CDI is defined as the recurrence of CDI symptoms within 8 weeks after symptom resolution, confirmed with a positive stool test. The risk of recurrence after an initial episode of CDI is 20% and increased up to 60% after the third episode [Khanna *et al.* 2012b]. The risk of recurrence is higher with older age, concomitant antibiotic exposure, presence of comorbidities and deceased levels of serum IgG anti-toxin A [Hu *et al.* 2009]. The first recurrence is treated the same as the first episode, stratified by severity. A second recurrence is treated with a 6–week taper of oral vancomycin. Several treatment options are available for future recurrences, which include FMT, vancomycin followed by rifaximin chaser or IVIG (Table 2). A case series of three patients demonstrated that fidaxomicin may be

an option for patients with multiple recurrences of CDI who have failed other therapies [Johnson and Gerding, 2013]. Although these options have not been compared in randomized clinical trials, fecal transplantation appears to be the most successful modality for recurrent CDI.

Conclusion

Over the past decade, the incidence and severity of both hospital- and community-acquired CDI has increased significantly. There is an emerging population who may contract CDI without the traditional risk factors and several novel risk factors have been identified. PCR based testing is highly sensitive and repeat testing is usually not advised after an initial negative test, or to confirm clearance after treatment in a patient who has responded symptomatically. In a patient with recurrent diarrhea, repeat testing should be performed to distinguish recurrent infection from other causes, such as postinfectious irritable bowel syndrome. Treatment strategies are based on severity and severe infection must be treated with oral vancomycin. Recurrent infection continues to be a major challenge and newer treatment options such as FMT may become the mainstay for recurrent CDI.

Funding

This review article was written without any specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

S.K. and D.S.P. have served as consultants for Optimer Pharmaceuticals.

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