Indian J Gastroenterol (November–December 2011) 30(6):245–254
DOI 10.1007/s12664-011-0148-y

REVIEW ARTICLE

Clostridium difficile infection: clinical spectrum and approach to management

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Received: 24 May 2011 / Accepted: 17 November 2011 / Published online: 20 December 2011

Abstract *Clostridium difficile* is recognized globally as an important enteric pathogen associated with considerable morbidity and mortality due to the widespread use of antibiotics. The overall incidence of *C. difficile*-associated diarrhea (CDAD) is increasing due to the emergence of a hypervirulent strain known as NAP1/BI/027. *C. difficile* acquisition by a host can result in a varied spectrum of clinical conditions inclusive of both colonic and extracolonic manifestations. Repeated occurrence of CDAD, manifested by the sudden re-appearance of diarrhea and other symptoms usually within a week of stopping treatment, makes it a difficult clinical problem. *C. difficile* infection has also been reported to be involved in exacerbation of inflammatory bowel diseases. The first step in the management of a suspected CDAD case is the withdrawal of the offending agent and changing the antibiotic regimens. Antimicrobial therapy directed against *C. difficile* viz. metronidazole for mild cases and vancomycin for severe cases is needed. For patients with ileus, oral vancomycin with simultaneous intravenous (IV) metronidazole and intracolonic vancomycin may be given. Depending on the severity of disease, the further line of management may include surgery, IV immunoglobulin treatment or high dose of vancomycin. Adjunctive measures used for CDAD are probiotics and prebiotics, fecotherapy, adsorbents and immunoglobulin therapy. Among the new therapies fidaxomicin has recently been approved by the American Food and Drugs Administration for treatment of CDAD.

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Keywords Clinical spectrum · *Clostridium difficile* · Diagnosis · Histopathological changes · Management

Introduction

Clostridium difficile is recognized globally as an important enteric pathogen associated with considerable morbidity and mortality. With the widespread use of antibiotics, *C. difficile*-associated diarrhea (CDAD) has become a common problem with pronounced medical and economic effects. A case of *C. difficile* infection is defined by the presence of symptoms (usually diarrhea) and either a stool test positive for *C. difficile* toxins or toxigenic *C. difficile*, or colonoscopic or histopathologic findings revealing pseudomembranous colitis (PMC) [1].

CDAD comprises 20% to 30% of antibiotic-associated diarrhea (AAD) with mortality up to 25% in frail elderly patients [2]. Antibiotic therapy causes alteration of the colonic microflora with multiplication of *C. difficile* in the large bowel and release of toxin A and toxin B responsible for the pathogenesis of CDAD. This is particularly important for surgeons because the most frequent indication for antibiotic use is perioperative prophylaxis, and surgical patients comprise 55% to 75% of CDAD patients [3].

The overall incidence of CDAD is increasing. CDAD is most common in hospital settings mainly due to clustering of cases in hospitals and within hospital wards. Dissemination of *C. difficile* occurs due to diarrhea and they exist in the hospital environment for a long time due to spore formation. Elderly patients undergoing antibiotic therapy for surgical procedures are at great risk of acquiring the infection. Even young immunocompromised patients are at constant risk due to impaired immune condition. The various factors of the hospital environment that may

contribute to the occurrence and transmission of this infectious agent include physical proximity of patients, environmental contamination, clustering of susceptible hosts and multiple person-to-person contacts. The exact cause for variability in response to *C. difficile* infection is not known, but host factors appear to be more important than bacterial virulence factors. An association between the *C. difficile* strains, production of toxins and clinical manifestation of the infection might exist.

Transmission

C. difficile is present in the feces of both patients and carriers, and transmission of the organism is by the feco-oral route. About 15% to 75% of healthy neonates are reservoirs for toxigenic *C. difficile*. Apart from this, the rate of asymptomatic carriage is 3% to 5% in healthy adults [4], and is up to 30% in patients receiving antibiotics or in those who are hospitalized [5]. Most CDAD strains are exogenously acquired from the hospital environment by touching of objects or surfaces contaminated with feces. It can also be transmitted by health care workers through contact with contaminated patients or their feces.

Recent studies also document airborne spread of *C. difficile* [6]. The incubation period of *C. difficile* infection is not precisely known. In most patients, infection manifests within 7 days after spore ingestion. However, the incubation period can be prolonged up to 4 weeks.

Clinical spectrum

Colonic manifestations

(1) **Asymptomatic carriage:** *C. difficile* ingestion may result in asymptomatic carriage; this may occur after recent antibiotic exposure or when there has been a previous CDAD episode. Colonization is common and occurs in 10% to 16% of hospitalized patients in high-risk units after receiving antibiotics [7]. Though most *C. difficile* isolates produce toxin, symptomatic disease is not often seen in carriers. It has been postulated that asymptomatic carriers of *C. difficile* contribute to the transmission of CDAD in long-term care facilities. Patients with *C. difficile* colonization and having an adequate specific serum immunoglobulin (IgG) response to *C. difficile* enterotoxin, do not develop clinical disease, but remain as asymptomatic carriers.

(2) ***C. difficile*-associated diarrhea:** Diarrhea is generally self-limiting, may be mild to moderate, sometimes accompanied by lower abdominal cramps. Symptoms usually begin during or shortly after antibiotic therapy, but occasionally may be delayed for several weeks. *C. difficile* toxins (CDT) may be detected in feces, even though endoscopic and histological features are normal in patients with mild disease. Symptoms resolve with the discontinuation of antibiotics.

(3) ***C. difficile* colitis:** Colitis without pseudomembrane formation is the most common clinical manifestation and is a more serious illness than benign or simple AAD. The common symptoms are malaise, abdominal pain, nausea, anorexia and watery diarrhea. Sometimes dehydration may occur along with low-grade fever. Systemic polymorphonuclear (PMN) leukocytosis may also be seen.

Lactoferrin levels are often elevated in patients with advanced CDAD as compared to those with mild disease. Simultaneous fecal lactoferrin assay along with CDT toxin assay can help rule out asymptomatic carriage of *C. difficile* [8]. Sigmoidoscopy may reveal nonspecific diffuse or patchy erythematous colitis without pseudomembranes.

(4) **Pseudomembranous colitis** (PMC) as a postoperative complication of gastroenterostomy was first described by Finney in 1893 in a 22-year old woman who underwent surgical resection of a gastric tumor. During sigmoidoscopy, PMC can be visualized as raised yellow plaques, a few centimeters in diameter, scattered over the colorectal mucosa. Sometimes these plaques coalesce to form the classical pseudomembrane. Most commonly, the rectosigmoid area is involved in most patients with PMC. But in approximately one-third of the patients, the pseudomembranes are limited to the proximal colon [9]. Histopathologically, fibrinous exudate containing lymphocytes, epithelial cells and mucin can be seen. PMC is the typical manifestation of full-blown *C. difficile* colitis and is accompanied by more severe symptoms than those observed in nonspecific colitis.

In severely ill patients, elevated white blood cell (WBC) count (>20,000/mL) and hypoalbuminemia (serum albumin <3.0 g/dL) may be observed [10]. Neutrocytic ascites with low serum-to-ascites albumin gradient may occur in patients with hypoalbuminemia [11]. At times ascites may be the only presenting manifestation of PMC [11].

(5) **Fulminant colitis:** Severe lower quadrant or even diffuse abdominal pain accompanied by distension and diarrhea may be seen in patients with fulminant colitis. Some patients may have high fever, chills and marked leukocytosis. Fulminant colitis due to *C. difficile* infections occurs in 3% to 8% of CDAD patients [12]. It accounts for most of the serious complications including perforation, pro-

longed ileus, megacolon and death. Diarrhea may be minimal in patients with ileus, resulting in accumulation of secretions in the dilated, atonic colon. A patient with toxic megacolon presents with signs and symptoms of severe toxicity, such as fever, chills, dehydration and high PMN blood count.

Dilated small intestine with air-fluid levels mimicking intestinal obstruction, ischemia or pseudo-obstruction may be seen on plain abdominal radiograph [13]. In such patients, barium enema examination is not advocated due to the risk of perforation and precipitation of megacolon [13], though computed tomographic (CT) scan of the abdomen is useful. In severe cases and in lesions localized to the proximal colon, CT scan may reveal colonic distension, thickening, pericolonic inflammation or free air. In some patients with fulminant *C. difficile* infection, signs and symptoms of bowel perforation may be present. Cecal perforation is imminent when the transverse diameter reaches 9 cm [14]. Aggressive diagnostic and therapeutic interventions may prevent further morbidity and mortality in patients with fulminant *C. difficile* colitis. Limited flexible sigmoidoscopy or colonoscopy may be performed at the bedside.

(6) **Recurrent CDAD:** Recurrent CDAD is manifested by the sudden re-appearance of diarrhea and other symptoms usually within a week of stopping *C. difficile* treatment. Repeated occurrence of CDAD makes it a difficult clinical problem, the pathophysiology of which is unclear. It may be due to persistently altered fecal flora by repeated antibiotic treatment leading to overgrowth of *C. difficile* or due to impaired immune response. In some patients, re-infection can occur with the same or different strain suggesting that relapse is generally not related to antibiotic resistance.

The small bowel and the appendix may also act as reservoirs of *C. difficile* spores that enter the colon and result in relapse [15]. Approximately 15% to 20% of patients relapse following successful therapy for CDAD. Further relapses are common after an initial relapse. McFarland et al. [16] reported a relapse rate of 65% in patients who had suffered two or more previous relapses.

(7) **Exacerbation of inflammatory bowel disease:** *C. difficile* infection has been reported to be involved in the exacerbation of ulcerative colitis [17, 18]. Balamurugan et al. [19] reported overgrowth of *C. difficile* in the stool of patients with ulcerative colitis. An alarming increase in incidence and severity in the course of *C. difficile* infections in patients with inflammatory bowel disease (IBD) with increased morbidity and mortality is being reported from the United States. Hookman and Barkin [20] observed that fulminant colitis is reported more frequently during outbreaks of *C. difficile* in patients with IBD and carries higher mortality than those without underlying IBD.

The prevalence of *C. difficile* among ulcerative colitis patients has been reported [21] to be 37.3/1000 and was higher than that among Crohn's disease patients (10.9/1000). In a recent retrospective study [22] in a tertiary care hospital over a 7-year period (1998–2004), the prevalence of CDAD in Crohn's disease doubled (9.5 to 22.3/1000 admission) and that in ulcerative colitis tripled (18.4 to 57.6/1000 admissions). In a study of 109 IBD patients, 99 diarrheic controls and 77 hospital outpatient controls, *C. difficile* positivity in IBD patients in remission was similar to that of patients in relapse. Overall 28% of IBD patients admitted to hospital in one year had at least one positive *C. difficile* stool result.

Greenfield et al. [23] and Issa and Ananthakrishnan [24] reported that over half of *C. difficile*-infected IBD patients would require hospitalization and that the colectomy rate would approach up to 20% in the near future. *C. difficile* infection should, therefore, be included in differential diagnosis for patients with refractory IBD as such patients do not necessarily have a history of antibiotic use or hospitalization, and most of them are treated as outpatients. IBD patients are known to be at increased risk for *C. difficile* enteritis as well as infections in reconstructed ileal pouch-anal anastomosis. In a pediatric study, 10% of all IBD patients who relapsed were positive for *C. difficile* [25]. Boland and Thompson [26] reported a case of *C. difficile* enteritis in a 42-year old man with ileo-anal pouch. Flexible endoscopy revealed copious amounts of mucus with adherent pseudomembranes throughout the ileal pouch as well as in the distal small bowel. Navaneethan and Giannella [27] reported that small bowel involvement is more frequently reported in IBD patients who have undergone total colectomy or in patients with ileo-anal anastomosis.

Extracolonic features

Earlier *C. difficile* infection was thought to be confined to the colon, but recent literature reveals that CDAD goes much beyond this limitation. Even though most of the cases do not appear to be strongly related to previous antibiotic exposure (except for cases of bowel involvement and reactive arthritis), they are by and large preceded by specific or nonspecific gastrointestinal (GI) disease, such as *C. difficile* colitis or surgical or anatomical disruption of the colon. The extracolonic manifestations due to *C. difficile* infection are as follows:

(1) **Small bowel involvement:** *C. difficile* enteritis seems to be increasing in incidence; 26 cases have been published recently [26]. The increase in the number of these patients may actually reflect an increase in the rising incidence of *C. difficile* infection in general or increase in virulence of the organism. Small bowel CDAD, with formation of pseudomembranes on ileal mucosa, may occur when previous ileal surgery has been done. It carries a high mortality rate.

(2) **Other manifestations:** *C. difficile* may cause bacteremia which has 20% mortality. Of the 15 cases reported in literature, 10 had polymicrobial *C. difficile* bacteremia and 6/15 patients died. The first case of *C. difficile* bacteremia was reported in 1962 in a 5-month old baby with cough, coryza and anorexia [28]. Adult patients with *C. difficile* bacteremia had concomitant GI pathology, and two patients had underlying hematologic malignancies. Libby and Bearman [29] presented a case of monomicrobial *C. difficile* bacteremia in a 40-year old African-American woman with past history of dermatomyositis, but without any GI symptoms.

Fairweather et al. [30] reported a case of reactive arthritis associated with documented *C. difficile*-induced enterocolitis. Boice [31] reported a case of *C. difficile*-associated reactive arthritis in a 66-year old man treated with oral penicillin for tooth abscess. *C. difficile*-related oligoarticular and polyarticular arthritis may involve knee and wrist joints in about 50% of cases [32]. Arthritis begins at an average of 11.3 days after the onset of diarrhea and resolves over a period of average 68 days [33]. The arthritis may be migratory and appear as enthesopathy with tendon involvement. The exact mechanism of reactive arthritis in *C. difficile* infection is not clear. Systemic absorption of toxin with antibody production may be one of the mechanisms. *C. difficile*-induced reactive arthritis appears to be associated with HLA-B27 in 66% of patients [31]. Ducroix-Roubertou et al. [34] reported a case of a monoarticular arthritis of the left knee following PMC in a 45-year old man, 8 days after the onset of a *C. difficile* enterocolitis.

Other extracolonic manifestations due to *C. difficile* that have been reported include cellulitis, necrotizing fascitis, osteomyelitis, prosthetic device infections, intra-abdominal abscess, empyema, localized skin infections, etc. Appendicitis has also been reported as a rare clinical manifestation [35].

Histological changes

C. difficile infection results in distinguishing microscopic and gross lesions. The histologic features have been classified into three distinct types [36]. The earliest lesions consist of focal areas of epithelial necrosis with neutrophil infiltration (type I lesions). A shower of fibrin and neutrophils erupts from the mucosal surface, and initiation of plaque formation occurs by the breakdown of epithelial lining and exudative eruption into the lumen. Type II lesions consist of a well-demarcated group of disrupted crypts, which get distended by mucin, neutrophils and eosinophils.

The epithelial damage extends to involve the lower part of the crypts, which is progressively lost. A few fibrin thrombi appear in the superficial mucosal capillaries. Focal mushroom-shaped volcanic eruptions of pseudomembrane attach to the necrotic mucosa. In type III lesions, the lamina propria becomes edematous and bulges into the colonic lumen. Focal congestion and hemorrhage in the lamina propria result in extravasation of blood into the intestinal lumen. Apart from the characteristic mucosal lesions, marked diffuse mural edema extending into the muscularis propria becomes evident [37]. Distinguishing *C. difficile* colitis from other forms of colitis is difficult when mucosal necrosis becomes confluent.

Diagnosis

C. difficile-associated diseases can be suspected and/or diagnosed clinically, endoscopically, radiologically as well as by identification of etiological agent and by toxin assays.

Clinically, the disease is diagnosed by the presence of profuse watery, green, foul smelling or bloody diarrhea along with abdominal cramps. Peripheral blood PMN leucocytosis and increased number of fecal leucocytes are other important features. Fever, if present, ranges from 38–39°C.

Endoscopically, PMC can be detected as multiple yellow-white friable plaques, attached to the underlying mucosa and biopsy taken helps to confirm the disease histologically. Endoscopy should be avoided in patients with paralytic ileus or colonic dilatation because of the risk of perforation. On radiological imaging, diffusely thickened or edematous colonic wall with pericolonic inflammation can be seen at CT scan and prompts strong consideration for initiation of specific therapy.

Toxigenic culture for *C. difficile* by growth on selective media, such as cefoxitin, cycloserine, fructose agar followed by toxin assay can be done to identify the etiological agent. PCR detection of toxin A and B genes is a highly sensitive (96%) and specific (100%) method; however, culture is initially required, which makes it more cumbersome. Presently, the most common method used is the enzyme immunoassay (EIA) that can detect both toxins A and B in stool specimens. EIA has sensitivity and specificity ranges of 70% to 90% and 70% to 95%, respectively.

Factors precipitating CDAD

Several factors determine whether or not a patient develops a *C. difficile* infection. An in-depth review on established and potential risk factors for CDAD has recently been published [38]. The factors can be categorized as follows:

(1) **General factors:** These include (a) long duration or multiple antibiotic intake (b) nature of the fecal flora (c) size of the *C. difficile* population (d) production of requisite cytotoxins (e) presence of other organisms that affect toxin expression or activity and (f) presence of host risk factors.

The host risk factors for acquiring a CDAD are innumerable. Prominent factors are advanced age, presence of a nasogastric tube, severe underlying illness, prolonged hospital stay, use of enemas, GI stimulants and stool softeners. Patients are at continuous risk of exposure to *C. difficile* during the period of hospitalization and become vulnerable to infection after exposure to antimicrobials. Thus, the two most important components essential for CDAD is exposure to antimicrobials followed by exposure to *C. difficile.* But the majority of patients exposed to these two components do not get ill unless a third additional factor related to host immunity, virulence of infecting *C. difficile* strain and timing of exposure come into play.

(2) **Medication-related factors:** Apart from antimicrobials, immunosuppressive drugs have also been reported to be associated with CDAD development [39]. Patients receiving immunosuppressive drugs are debilitated and, therefore unable to mount an effective IgG antibody response against *C. difficile* toxin A, thereby increasing the risk for CDAD. *C. difficile* colonization is more frequent in intensive care and oncology units, where broad spectrum antibiotics and immunosuppression are widespread. Another important CDAD precipitating factor is the use of gastric acid suppressive drugs [40]. These drugs raise the pH of the stomach resulting in an increased risk of CDAD [40]. Proton pump inhibitors may, thus contribute to the CDAD pathogenesis due to increased survival of spores.

Administration of cancer chemotherapeutic agents possessing antibacterial properties may also result in sufficient disturbance of the intestinal microflora to allow *C. difficile* colonization. Exposure to corticosteroids was also significantly associated with an increased risk of CDAD relapse [41].

Thus, the combination of the environmental presence of *C. difficile* in health care settings and the number of people receiving antibiotics, immunosuppressives, proton pump inhibitors or cancer therapeutics in these settings can result in frequent outbreaks. Zerey et al. [42] demonstrated that the incidence of *C. difficile* infection was increasing in surgical patients in United States and was most prevalent after emergency operations particularly among patients having intestinal tract resections.

(3) **Emergence of a hypervirulent strain:** *C. difficile* is getting more difficult than ever! What was initially believed to be just a clinical nuisance has turned out to be a real bioterrorist. CDAD has become a matter of grave concern in hospital environments since 2001 due to the emergence of a hypervirulent fluroquinolone resistant epidemic strain known as NAP1/BI/027. This strain produces approximately 16-fold more toxin A and 23-fold more toxin B in vitro. It also produces the 'binary toxin', the pathogenic role of which is not yet clear. The increased incidence of nosocomial CDAD in the West with marked increase in severity of cases requiring colectomy or ending in death was attributed to the liberal use of fluroquinolones and cephalosporins.

The NAP1/BI/027 strain poses a great risk as it is also found to be resistant to the newer broad spectrum fluroquinolones, such as moxifloxacin. In 2007, severe cases of CDAD with this epidemic strain were detected in Germany for the first time and were strongly associated with receipt of cephalosporins and fluroquinolones in the 3-month before onset of symptoms [43]. Metronidazole treatment failure before 2004 was reported to be about 0% to 6% in 4 trials but after 2004 treatment failure was reported in about 16% to 38% in 3 different trials [44]. Similarly in 2005, vancomycin treatment failures reported was 19% with CDAD recurrence in 37% [44]. The incidence of PMC, toxic megacolon and perforation in *C. difficile* infection was rare in 2002. In 12 hospitals in Quebec, there was a 3-fold rise in CDAD and increased cases involving toxic megacolon, colectomy and death [45]. The NAP1 strain was identified in 8 institutions in 6 different states of USA and more than 80% affected with CDAD were over 65 years. This global strain has been reported from United Kingdom, Netherlands, Belgium, France, Austria, Luxembourg, Poland, Japan, Finland, etc. and the community cases of *C. difficile* infection are also increasing. Apart from this, another ribotype 078, a strain frequently isolated from the intestines of pigs and calves has also been observed to be increasing in Europe [46].

The Indian scenario

C. difficile associated diarrhea is prevalent globally, but its incidence varies from place to place. Gupta and Yadav

[47] were the first to detect *C. difficile* in 25.3% diarrheal patients of all age group. This was followed by a study from Ayyagari et al. [48] who reported the presence of *C. difficile* in 22.6% stool specimens obtained from cases of antibiotic associated colitis with or without pseudomembranes.

Niyogi et al. [49] reported *C. difficile* in 8.4% and cytotoxin in 7% of fecal samples in pediatric age group. In hospitalized patients with diarrhea, they reported a prevalence of 11% [50]. Bhattacharya et al. [51] investigated 233 patients with acute diarrhea and isolated *C. difficile* as a sole pathogen from 7.3%, of which 82.3% produced cytotoxin. Vaishnavi et al. [52] reported a positive CDT assay in 30% patients in the antibiotic receiving group compared to only 7% in those not receiving the antibiotics. In addition to this, fecal lactoferrin assay was found to be a useful adjunct for CDAD diagnosis as evaluation in adult patients showed highly significant relationship between CDT and fecal lactoferrin assay [53]. In the pediatric group, no significant relationship between antibiotic usage and diarrhea was seen; however, CDT positivity was influenced by antibiotics, and the relationship between CDT and fecal lactoferrin was significant [53]. Kang et al. [54] reported that CDAD was more common in the post transplantation period in India than in other developed countries. Vaishnavi et al. [18] reported increased prevalence of diarrhea after antibiotic usage in the ulcerative colitis group. Psoriatic patients given either methotrexate or mesalamine had increased *C. difficile* carriage [55]. Gogate et al. [56] reported *C. difficile* as an important pathogen in younger children with AAD. Chaudhry et al. [57] reported a decrease in the number of *C. difficile* positive cases during a five year study period due to stringent surveillance and improved antibiotic policy adopted by the hospital. Ingle et al. reported CDT positivity in 17 of 99 patients with diarrhea. As compared with control subjects, patients with CDAD more often had fever, prolonged ICU stay, underlying malignancy, and exposure to immunosuppressive and chemotherapeutic agents; on multivariate analysis, exposure to immunosuppressive agents was the only risk factor associated with CDAD [58].

Management

The first step in the management of a suspected CDAD case is withdrawal of the offending agent and isolation of the patient. This form of management often helps, but antibiotic discontinuance is not always possible in the critically ill hospital patient. Therefore, changing the antibiotic regimens is recommended. Thus, the ironic twist of standard treatment for *C. difficile* infection is in fact another antibiotic!

Attention should be paid to fluid replacement and electrolyte balance as is done for other cases of diarrhea. Opiates and antiperistaltic drugs are generally avoided because they obscure symptoms and may even precipitate toxic megacolon. About 25% respond within a few days to this line of treatment [59]. Exacerbation of IBD due to *C. difficile* colitis may occur; therefore, empiric treatment with corticosteroids without appropriate antibiotics may lead to deterioration. IBD patients with *C. difficile* infection require longer hospital stays with increased costs and more complications including colectomy and the need for more aggressive immunosuppression.

Therapeutic management

For mild cases, antimicrobial therapy directed against *C. difficile* is needed. Oral metronidazole, 400/500 mg, three times daily for 10–14 days is recommended as the initial therapy of choice. With this, diarrhea generally gets resolved in 1–2 weeks in 80% of the patients. However, recurrence may occur for the first time in approximately 20% of the patients and a subsequent relapse in 50% to 60%. It should be borne in mind that oral vancomycin is not cost effective and there is the risk of selection of vancomycin resistant enterococci.

Therefore, metronidazole is preferred as the initial agent of treatment for a CDAD. However, if the symptoms are not improving or have worsened, then oral vancomycin 125 mg four times a day for 10–14 days is recommended. Oral vancomycin is the drug of choice if the patient is having severe CDAD with a white cell count of more than 15,000/mL, raised creatinine level (i.e., 150% above baseline) and symptoms of colitis. For patients with ileus, oral vancomycin 125–500 mg four times a day along with simultaneous IV metronidazole 500 mg thrice daily for 10 days and intracolonic vancomycin 500 mg in 100–500 mL saline may be given 4–12 hourly. Depending on the prognosis, the line of further management may include surgery, IV immunoglobulin treatment or high dose of vancomycin. Colectomy should be done if the serum lactate increases above 5 mmol/L and the peripheral WBC count is more than 50,000/mL [60]. Ben-Horin et al. [61] reported improvement in the clinical outcome of CDAD in patients with pre-existing inflammatory bowel disease treated with immunomodulators, such as anti-tumor necrosis alpha.

Recurrent CDAD cases have been managed by some workers by pulsed dose therapy or extended interval vancomycin therapy. In pulsed dose therapy, vancomycin is administered in short intermittent courses by decreasing or increasing the dose. This is based on retrospective data. The extended interval vancomycin program is based on the hypothesis that prolongation of vancomycin treatment from

2 weeks to 4 weeks will lead to a decreased rate of recurrence as a 2-week duration could be inadequate in clearing the infection.

Adjunctive measures for CDAD

The increase in the rate of incidence, mortality and morbidity due to CDAD over the past decade has stimulated a search for newer kinds of therapeutic management apart from the standard treatment given for CDAD.

(1) **Probiotics and prebiotics:** Several different probiotics have been used from time to time to treat *C. difficile* infection. They are *Lactobacilli rhamnosus* GG, *Lactobacillus acidophilus, Saccharomyces boulardii, Bacillus clausii, Bifidobacterium longum*, *Clostridium butyricum, Enterococcus fecium* SF68 and nontoxigenic *C. difficile.*

Four studies examined probiotic use in conjunction with vancomycin/metronidazole for treatment of initial episode or recurrence of CDAD in adults [62]. But there is insufficient evidence to recommend probiotic therapy as an adjunct to antibiotic therapy for *C. difficile* colitis. There is no evidence to support the use of probiotics alone in the treatment of *C. difficile* colitis. Probiotics only help to restore healthy balance to the intestinal tract. Also, one case series observed invasive fungemia with the use of *Sachharomyces cerevisae* and it is a deterrent for use in elderly, immunocompromised patients with increased colonic permeability due to CDAD [62].

Prebiotics, such as inulin and oligofructose have also been used as adjunct therapy as they stimulate the growth of beneficial bacteria in the colon [63]. Lewis et al. [64] reported lesser CDAD relapse when oligofructose was combined with either vancomycin or metronidazole.

(2) **Fecotherapy:** Fecotherapy involves rectal instillation of donor stool or mixed broth cultures given as enema, colonoscopy or nasoduodenal tube to restore the colonization barrier of the gut. This treatment has been used in uncontrolled studies in Scandinavia [65].

(3) **Adsorbents:** Ion exchange resins, such as cholestyramine and colestipol have been used from time to time as adjunctive treatment as they bind to *C. difficile* toxins in the colonic lumen before they can attach to the enterocytes and induce disease. Oligosaccharide sequences attached to inert silica based support (Synsorb 90) works as a decoy toxin receptor. Tolevamer is another high molecular weight polymer that binds to the toxins of *C. difficile* and blocks their activity.

Louie et al. [66] conducted a multicenter Phase II trial comparing 3 g and 6 g doses of tolevamer (14 days) with 500 mg vancomycin (10 days) in patients with CDAD. They found that 6 g dose of tolevamer was non-inferior to vancomycin for treatment of mild to moderate CDAD. However, hypokalemia was found to be associated with tolevamer therapy. A Phase III trial comparing a higher dose tolevamer (reformulated to include potassium) with vancomycin and metronidazole [67] showed that tolevamer did not meet its primary endpoint of non-inferiority compared to vancomycin, even though recurrent CDAD was uncommon with tolevamer suggesting that flora-sparing drugs may help reduce recurrences.

(4) **Immunoglobulin therapy:** Leung et al. [68] used IV immunoglobulin (IVIg) for the first time to treat CDAD. Recently, Abougergi et al. [69] reported treatment with IVIg (200 mg/kg to 1,250 mg/kg for 1–3 days) in 21 patients with severe CDAD. Nine patients survived with complete clinical resolution within 2–20 days. The other 12 patients died during the index hospitalization, suggesting that the benefit of IVIg depended on the extent of systemic involvement. IVIg treatment should only be given if the albumin status worsens. Thus, it appears that more studies are required on the ideal timing and dose of IVIg administration, as well as patient selection, before IVIg administration can be included in CDAD management strategy. IVIg is yet to be approved by the US Food and Drug Administration and is not easily available.

(5) **Monoclonal antibodies:** Lowy et al. [70] examined the safety of monoclonal antibodies and its effects on the duration and severity of the initial episode of CDAD and on duration of hospitalization in a Phase II randomized, double-blind, placebo-controlled trial. The fully human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1) together were administered as a single infusion at a dose of 10 mg/kg body weight to 101 patients who were receiving either metronidazole or vancomycin and to 99 placebo receiving controls. The combined administration of both the monoclonal antibodies in addition to antibiotics significantly reduced the recurrence of CDAD.

(6) **Bovine antibodies:** van Dissel et al. [71] investigated the feasibility of immune whey protein concentrate (4%) made from milk after immunization of Holstein-Frisian cows with *C. difficile* inactivated toxins and killed whole *C. difficile* cells for CDAD management. They reported that immune whey protein concentrate-40 may help in prevention of relapse of CDAD.

(7) ***C. difficile* vaccine:** Aboudala et al. [72] reported intramuscular inoculation of vaccine produced from culture filtrate antigen toxoid A and toxoid B to 30 healthy volunteers with a 50-fold increase in serum

antitoxin A production. Souigioltzis et al. [73] reported that two of three patients with recurrent CDAD showed increase in serum IgG to toxin A with no further recurrence upon discontinuance of treatment with vancomycin. Administration of *C. difficile* vaccine could lead to promising strategies for prevention and treatment of CDAD. Presently, it is undergoing Phase III trial in United Kingdom.

(8) **New therapies** under evaluation are as follows:

(a) **Nitazoxanide:** Nitazoxanide, a broad spectrum antiparasitic drug is also active against *C. difficile* achieving high colonic level. A multicentric randomized study with nitazoxanide (7 days) versus metronidazole (10 days) showed that nitazoxanide is non-inferior to metronidazole therapy for mild to moderate CDAD [74].

(b) **Rifaximin:** Rifaximin is a poorly-absorbed rifamycin derivative used for the treatment of recurrent CDAD with high percentage of drug resistance. This suggests that exposure to rifamycins before the development of CDAD is a risk factor for rifampin-resistant *C. difficile* infection.

(c) **Ramoplanin:** Ramoplanin has been found to be effective against *C. difficile*. In Phase II trial of 86 CDAD patients receiving either 200 or 400 mg of ramoplanin twice daily or 125 mg vancomycin four times daily for 10 days, each group had similar rates of cure at 28 days [67]. Ramoplanin may be useful for future treatment of CDAD and a Phase III trial is currently ongoing.

(d) **Tigecycline:** This glycylcyclin IV antibiotic has been found to be associated with lower risk of CDAD and appeared as a useful salvage therapy in a case series of patients with severe CDAD complicated by ileus [75].

(e) **Fidaxomicin:** Louie et al. [76] studied 629 adults with CDAD who were randomly assigned to receive 200 mg fidaxomicin or vancomycin for 10 days. The rates of clinical cure with fidaxomicin were non-inferior to those after treatment with vancomycin. Fidaxomicin has been recently cleared by the American FDA for treatment of CDAD.

Infection control measures

Precaution should be taken, such as washing hands with soap and water frequently between entering patient's room and after each contact with patient and his environment. Using of hand gloves and gowns when soiling is anticipated during patient care, dedicating equipments separately to patients, maintaining precautionary measures for at least three days after the diarrhea has resolved is highly recommended for CDAD patients. The endoscope should be disinfected after each use and rectal thermometers should be put to only single use. For environmental cleaning and disinfection, an approved hospital grade disinfectant, such as sodium hypochlorite, glutaraldehyde, peracetic acid, chlorine, etc. must be used. All patients with active *C. difficile* infection should be isolated in single rooms with barrier precautions. Restriction policy for high-risk antibiotics should be strictly followed.

Conclusions

C. difficile-associated diarrhea has become a common problem with pronounced medical and economic effects, more so after the emergence of the NAP1 strains. It is very difficult to eradicate *C. difficile* from the hospital due to dissemination of spores in the hospital environment. *C. difficile* acquisition can result in a varied spectrum of enteric diseases, both symptomatic and asymptomatic. Asymptomatic *C. difficile* colonization should not be treated. To avoid precipitation of CDAD, use of narrow-spectrum antibiotics should be encouraged. Oral metronidazole is the drug of choice for an initial CDAD episode.

Oral vancomycin is an option for patients who cannot take or fail treatment with oral metronidazole. First-time recurrences should be re-treated with the same regimen used to treat the initial episode. Clinicians must avoid vancomycin wherever possible, and not treat nosocomial diarrhea empirically without testing since even during outbreaks, less than 30% have CDAD. Reducing the use of injectable cephalosporins leads to significant reduction in CDAD cases. Combined approach of infection control and strict antibiotic policies can go a long way in reducing the burden of CDAD.

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