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Clostridium difficile infection in patients with inflammatory bowel disease

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Abstract

Clostridium difficile infection in patients with inflammatory bowel disease has become a serious clinical problem over the past few years. This review is focused on the current changes in epidemiology, pertinent clinical aspects, standard and newer diagnostic methods, established and novel therapies, and prevention of infection. There is emphasis on the importance of clinical awareness, rapid detection by stool testing, and appropriate antibiotic therapy, while newer technologies, antibiotics and other treatments are explored.

Keywords *Clostridium difficile, ulcerative colitis, Crohn's disease*

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Introduction

Clostridium difficile, an anaerobic spore-forming Gram-positive bacillus found commonly in the environment, was recognized since 1978 as an important cause of nosocomial diarrhea in hospitalized patients receiving antibiotics for a variety of infections, and was often difficult to diagnose and treat. This was found to be a paradoxical disease; it occurred in patient receiving antibiotics in hospitals, and was then treated by use of antibiotics. The past decade has seen a dramatic change in the epidemiology of *C. difficile* infection [1]. Nowadays there is often no history of antibiotic use in those cases arising outside hospitals. There has been an increase in the severity of disease associated with *C. difficile*, and outbreaks with the toxinotype III B1/NAP1/027 strains were documented worldwide [2]. Of great concern, a sharp rise in the rate of *C. difficile* infection in patients with inflammatory bowel disease (IBD) has being reported in recent years [3]. IBD remains an idiopathic condition, and comprises ulcerative colitis (UC) and Crohn's disease (CD) in a 2:1 ratio of occurrence. Prior antibiotic use is not detected in some 40% of *C. difficile* outbreaks in IBD, and many infections are in fact community-acquired. There is an alarming increase in morbidity, mortality, need for surgery, resource consumption and healthcare cost resulting from *C. difficile* colitis occurring in IBD patients compared with non-infected IBD subjects; therefore, *C. difficile* now presents an important public health issue for gastroenterologists. There appears to be a worse long-term course of IBD after *C. difficile* infection, but the mechanism whereby infection with *C. difficile* alters the natural history of UC and CD is unclear. It is uncertain whether *C. difficile* in IBD patients simply triggers symptoms that then resolve on resolution of the infection, or whether it causes a flare of intestinal inflammation that outlasts the organism's presence in the bowel [4]. With increasing incidence and severity of *C. difficile* colitis, the need for improved strategies for diagnosis, treatment and infection control cannot be overstated.

This article is devoted to the problem of *C. difficile* infection in adult and pediatric IBD patients in the context of understanding the magnitude of the problem, the diagnostic methods currently available, and treatment options.

Methods

A search was conducted of the English-language literature as indexed in PubMed over the last 15 years, using as index terms: *Clostridium difficile*, ulcerative colitis, Crohn's disease, inflammatory bowel disease. Relevant full-length articles were studied in detail, and form the basis for this review. The literature yielded more information about UC, this being the more prevalent form of IBD, than CD. In addition, pertinent presentations at recent (last three years) meetings

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of the Interscience Conference on Antimicrobial Agents and Chemotherapy attended regularly by two of the authors were perused, and some of this very new information was included. Indeterminate colitis was not researched.

Epidemiology of *C. difficile* infection in adults with IBD

The incidence of *C. difficile* infection in IBD has doubled in recent years, with marked impact on morbidity and mortality. Several recent epidemiological studies in the USA have examined hospital admission frequencies for *C. difficile* colitis. In a retrospective cohort analysis of IBD patients with co-existing *C. difficile* colitis in the USA Nationwide Inpatient Sample (a 20% stratified random sample of national hospital discharge abstracts from 1993 through 2003), it was found that the prevalence of *C. difficile* had increased significantly in patients with UC and colonic CD, although not in CD patients with disease limited to the small intestine [5]. Case fatality rose significantly when *C. difficile* was present in UC cases, but not in patients with CD. Operative mortality for UC patients with co-existing *C. difficile* approached 26%. Sonnenberg [6] reported a strong association of hospitalization rates in CD and UC respectively with the presence of *C. difficile* colitis. Likewise, there were correlations of the mortality rates in each type of IBD with *C. difficile* colitis. Each hospitalization rate also correlated with the corresponding mortality rate. A particular geographical distribution was noted as well, where hospitalization and mortality associated with IBD tended to be frequent in many of the northern states of the USA but infrequent in the southwest and southern states. This could have indicated an influence of *C. difficile* in shaping the geographic patterns of occurrence of UC and CD, although it was also possible that a common effect of the environment could have been influencing the occurrence of both types of IBD as well as the occurrence of *C. difficile* colitis. A third study of population-based trends in rates of *C. difficile* infection among hospitalized IBD patients in the USA showed a prevalence rate of *C. difficile* among UC patients of 3.7%, in CD patients 1.1%, and in non-IBD patients under 0.5% [7]. *C. difficile* rates rose among UC patients from 2.7% to 5.1% over the 7 year study period. *C. difficile* infection was associated with greater mortality among patients with UC (OR 3.8), but not CD. *C. difficile* was also associated with longer lengths of stay in hospital and greater charges in both forms of IBD. Lundeen et al reported a six-fold increase in the rate of positive *C. difficile* A and B toxin tests among inpatients at a major USA hospital in an uncontrolled observation covering the years 2000-2005 [8]. To estimate the potential excess morbidity and mortality resulting from *C. difficile* infection in hospitalized patients with IBD, data from the Nationwide Inpatient Sample were analyzed by Ananthakrishnan et al [9]. Of 124,570 hospital discharges in the year 2003, 2.3% were diagnosed as having both *C. difficile* and IBD, 36% *C. difficile* alone, and 62% IBD alone. On multivariate analysis, patients in the *C. difficile*-IBD group had a four times greater mortality than patients admitted for IBD alone (OR 4.7) or *C. difficile* alone (OR 2.2), and had extended hospital admission times. While UC patients had significantly higher mortality and surgery rates compared with CD, no differences in length of stay or hospital cost between these two diseases were noted. This is in no way a condition confined to the USA. The same clinical pattern has been documented in Canada and many European countries, so that there is really a worldwide epidemic.

C. difficile appears to predict recurrent flares in IBD patients. In a historical cohort study of patients admitted to hospital with an UC flare, 47 of 99 patients were positive for *C. difficile* [10]. Demographic data did not differ between positive and negative patients. However, positive patients had significantly more UC-related hospitalizations and emergency room visits in the year following initial admission. *C. difficile* patients had twice the rate of colectomy at one year following the index admission but there was no difference at initial admission. In another study, in 54 patients evaluated during 62 relapses of IBD with 99 stool samples, a pathogenic microbe, mainly *C. difficile*, was found in 20% of the IBD patients [11]. In these cases antibiotic use in the past month was significantly associated with detection of *C. difficile* toxin.

Fulminant *C. difficile* colitis can have a death rate upwards of 80%, so that treatment options should include subtotal colectomy since this may reduce mortality. Risk factors for higher mortality in *C. difficile* colitis were found to include a history of IBD, recent surgery, hypotension and leukocytosis [12]. *C. difficile* infection was fatal in the report by Shen et al of a 61-year-old woman who had undergone total proctocolectomy with ileal-pouch-anal anastomosis and a loop ileostomy for steroid-refractory ulcerative colitis [13]. Eight months later, after elective ileostomy closure, she succumbed to fulminant *C. difficile*-associated pouchitis and enteritis.

C. difficile is also reported in uncommon situations associated with IBD. It was detected occasionally in cases of small bowel enteritis, and carries a mortality rate of 60% or more. In this context it is interesting to note that Lundeen et al reported 6 patients aged 20-59 years who had received antibiotics before colectomy for UC, and all these patients developed severe *C. difficile* enteritis [14]. In four of these 6 patients *C. difficile* colitis was diagnosed before colectomy. Presenting symptoms of enteritis included high volume watery ileostomy diarrhea followed by ileus. All patients with enteritis responded to intravenous metronidazole followed by oral metronidazole or vancomycin. *C. difficile*-associated small bowel enteritis has also been reported in a CD patient following total proctocolectomy [15]. In a different setting, it should be noted that recurrent colitis in the rectal remnant after colectomy for UC is occasionally caused by *C. difficile* infection. Metronidazole suppositories have been efficacious in this setting [16].

C. difficile infection in children

Most literature on *C. difficile* has related to the adult population, but the disease is common in children as well.

The asymptomatic carriage rate is highest in infants and small children and then falls to about 5% in adults. Of note, IBD in children usually appears at over the age of 2 years. Morinville and McDonald have produced a timely review of the clinical findings in 200 Canadian infants and children (mean age 5.4, median age 2.6 years) with *C. difficile* infection [17]. In these cases, potential risk factors included CD (3.5%), antigastric secretory medication (28%), recent hospitalization (58%) and recent antibiotic use (74.5%, mostly for respiratory infections). A little over half of the cases presented with diarrhea while being outpatients. The diarrhea was bloody in 12.5% of cases. The mortality rate attributable to *C. difficile* was 1%. In a further pediatric study, stool specimens from 81 children with IBD and 112 without IBD were evaluated for the presence of *C. difficile* toxins [18]. The prevalence of *C. difficile* was significantly greater in the patients with IBD than in those without IBD. In the patients with IBD, the prevalence of active disease was significantly greater in the *C. difficile*-infected patients than in the uninfected patients. Colonic involvement was found in all patients with IBD. In light of the foregoing, noting the rising incidence of IBD now being documented in children, it has become important to consider co-infection with *C. difficile* in this age group as well.

Risk factors promoting *C. difficile* colitis

C. difficile infection is the most important cause of nosocomial diarrhea, and many antibiotics have been implicated as causing this condition, including in rare cases vancomycin and metronidazole (Table 1). It is important to identify early those patients who are at increased risk for acquiring *C. difficile* infection, such as older persons and those in hospitals or institutions. However, it should be emphasized that *C. difficile* infection has nowadays been reported in persons previously thought to be at low risk, such as young and healthy persons without exposure to health care settings or antibiotics, peripartum women, and in children. As stated above, in patients with IBD the chance of *C. difficile* infection is greater, although why this occurs is not understood. The emergence of a hypervirulent strain and other factors including antibiotic overuse seemed to have contributed to the escalating incidence and intensity of this infection [19,20]. The use of corticosteroids (but not other immunomodulators or anti-TNF) in IBD patients has been implicated in the causation of *C. difficile* colitis [21]. There is widespread use of proton pump inhibitors (PPI) for suppression of gastric acid secretion. While one report suggested that PPI use could provoke an increased rate of *C. difficile* infection [22], the issue is still controversial. Nonetheless, this issue requires vigilance given the wide use of PPI in hospitalized IBD patients, particularly where anticoagulation therapy is required.

Table 1 Common antibiotics precipitating *Clostridium difficile* colitis [19]

Frequent: Ampicillin, Amoxicillin, Clindamycin, Quinolones, Cephalosporins
Infrequent: Erythromycin, other macrolides, sulphonamides
Rare: Chloramphenicol, metronidazole, rifampin, tetracyclines, rifaximin, vancomycin

C. difficile testing

Stool testing for *C. difficile* should be performed in all patients presenting for the *first* time with a clinical picture suggestive of UC or CD as part of the initial process of establishing the diagnosis. It is highly recommended also in patients with flares of IBD, and especially when there is a slow or poor response to treatment, despite the added cost of performing the toxin assay, since misdiagnosis has serious consequences. Detection of *C. difficile* infection in IBD patients however is not easy, and there is no specific dependable clinical picture or stool characteristic such as the odor. The classic pseudomembranes appear as a confluent yellowish exudate in the rectum or colon, with biopsies showing the typical volcano lesions. Pseudomembranes were once a *sine qua non* for the colonoscopic diagnosis of *C. difficile* diarrhea. However, it has become obvious in recent years that some cases will not develop pseudomembranes, particularly the IBD patients. Many IBD patients will be taking long-term immunomodulatory treatments, particularly azathioprine, and pseudomembranes tend to be absent in immunosuppressed patients [23]. In a series of 4 patients with UC and 4 patients after hematopoietic stem cell transplantation, all presenting with *C. difficile* toxin A, none of the cases had pseudomembranes at colonoscopy. The lesson is that when UC becomes exacerbated or when patients present with diarrhea after transplantation, stool tests for *C. difficile* are required even in the absence of pseudomembranes. Furthermore, failure to detect toxin should not deter the gastroenterologist from initiating treatment when the index of suspicion is high.

Testing for *C. difficile* or its toxins should be done only on diarrheal (unformed) stools, unless ileus due to *C. difficile* is suspected. A single stool specimen per patient is usually sufficient, but swab specimens are unacceptable. The sample should be submitted to the laboratory promptly. Testing of stool from asymptomatic patients is not clinically useful and is not advised [24]. The cell-culture cytotoxic assay remains the gold standard for detection of *C. difficile*. However, the typical cytopathic effect appears only after 1-2 days. Anaerobic stool culture is not clinically practical due to its slow turnaround time [24]. Enzyme immunoassay (EIA) testing for CD toxin A and B, adopted by laboratories worldwide, is most important clinically because it is a rapid test, easy to use and with lower cost, but has a lower sensitivity (63-94%) and specificity (75-100%) than the "gold standard" cell-culture cytotoxin assay [24]. A potential strategy to overcome this problem includes a 2-step method that uses EIA detection of glutamate dehydrogenase (GDH), a *C. difficile* common antigen, as an initial

rapid screening with a high negative predictive value, and then uses another method that detects the toxin, such as the cell cytotoxin assay or toxigenic culture (culture followed by detection of a toxigenic isolate), as the confirmatory test for GDH-positive stool specimens only. More data are needed on the sensitivity of GDH testing [25-27]. As said, toxin testing is the mainstay of diagnosis of *C. difficile* infection. The organism produces two cytopathic toxins A and B that adhere to the mucosal epithelium and cause a variety of symptoms. Most laboratories today prefer the toxin A/B assay over the toxin A assay because 1-2% of strains are negative for toxin A, which is a problem since virulent strains with only toxin B secretion have been detected. Single toxin assays fail to detect a significant percentage of *C. difficile* infections [28]. In a study of 697 stool specimens from 284 IBD patients, toxin A assay failed to identify 42% of *C. difficile* infections, and toxin B assay 35% of infections. Furthermore, the toxin profile actually changed over time in 55% of the patients who experienced multiple infections. Therefore, whenever *C. difficile* infection is anticipated, toxins A and B should both be tested. In this scenario, the positivity rate after one EIA test (toxins A and B) is 88%, and reaches 96% on a repeat test [29]. One negative result should lead to repeat testing where the clinical suspicion is high, but further testing has a low sensitivity. Of note, there is no role for post-treatment stool testing to confirm eradication [30].

The use of PCR is an alternative newer diagnostic method worthy of consideration. PCR testing appears to be rapid, sensitive, and specific. Real-time PCR (RT-PCR) has been used on fecal samples from UC patients with *C. difficile* infection by Balamurugan et al [31]. Fecal DNA was extracted and quantitative PCR carried out with primers to amplify species-specific fragments of 16s rDNA of *C. difficile* and expressed as relative fold differences against highly conserved (universal segments); toxins A and B were assayed by ELISA. qPCR detected *C. difficile* in 34 of 37 (91%) patients with UC who not had been exposed to antibiotics, whereas the toxin test was positive in only 8 of the patients. The qPCR result was independent of the extent of colonic disease or level of activity of the colitis; therefore the significance of the high detection rate by PCR in these UC subjects was incompletely understood. Of interest, the detection rate of *C. difficile* rDNA in fecal samples from healthy volunteers was high at 56%. Clearly, more data on this method are necessary before it can be recommended for routine testing.

Disease severity

According to the IDSA/SHEA *C. difficile* infection guidelines [24], *C. difficile* infection severity criteria are as follows: mild to moderate, WBC <15,000 and creatinine <1.5 x patient's baseline; severe, WBC >15,000 or creatinine >1.5 x patient's baseline; severe complicated *C. difficile* infection, hypotension, shock, ileus, or megacolon due to *C. difficile* infection.

According to the ESCMID *C. difficile* infection guidelines [32], severe *C. difficile* infection is defined as an episode of infection with one or more signs of severe colitis. However, *C. difficile* infection without clinical signs of severe colitis may also be regarded as severe when detected in patients having the following risk factors: advanced age (≥65), serious comorbidity, admission to intensive care, or immunodeficiency.

Treatment of *C. difficile*

In IBD patients the early identification and treatment of *C. difficile* superinfection is clearly important to avoid serious outcomes. Oral (or intravenous) metronidazole (250-500 mg given 3-4 times per day for 10-14 days) and oral vancomycin (150-500 mg given 4 times per day for 10-14 days), in that order, have been the favored treatments for over 30 years, and offer 87% and 97% efficacy, respectively [19]. These drugs achieve adequate luminal concentrations in the colon and rectum. Metronidazole is preferred for milder disease, since its efficacy is high, drug resistance is still relatively low, and it is much cheaper. For persistent or recurrent cases, the usual measures include repeated courses of these drugs, alone or in combination, and tapered and pulsed courses of vancomycin. Vancomycin is used for treating *C. difficile* strains resistant to metronidazole and for more severe infections. For severely ill patients, simultaneous administration of high dosage metronidazole and vancomycin at the very beginning of therapy is recommended. Note that metronidazole is not to be used in pregnant and nursing women, and its safety in children has not been documented, whereas vancomycin can be given during pregnancy and to children. Vancomycin can be administered by nasogastric tube or in a saline retention enema if there is oral intolerance. There is some concern about the possible emergence of vancomycin-resistant enterococci [30]. Metronidazole suppositories may be useful for pouchitis complicated by *C. difficile* in addition to standard oral therapy.

The use of alternate antibiotics has been researched extensively, but no consensus has been reached. Nelson comprehensively reviewed twelve randomized, controlled trials (1157 participants) of antibiotic treatment for *C. difficile*-associated diarrhea involving patients who had recently taken antibiotics for other infections [33]. Eight antibiotics were studied, including vancomycin, metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin and bacitracin. In paired comparisons, no single antibiotic was superior to others, though teicoplanin, a costly antibiotic of limited availability, showed in some trials a significant benefit over vancomycin and fusidic acid, and a trend towards benefit compared with metronidazole. The combination of metronidazole and rifampin had no advantage over metronidazole alone. Teicoplanin is not readily available but was somewhat better than vancomycin for bacteriologic cure. Bacitracin was less effective. Nitazoxamide has been shown in a prospective, randomized, double-blind study (N=74) to be as effective as metronidazole in treating *C. difficile* colitis

[34]. Fidaxomicin is a bactericidal macrocyclic antibiotic that has been found to reduce *C. difficile* counts while, unlike vancomycin, maintaining *Bacteriodes* species, a major constituent of normal flora [35,36]. A phase III trial in 128 subjects who had experienced a single prior *C. difficile infection* episode and had recurred within three months, showed fewer recurrences and higher global cure rates in comparison to fidaxomicin with vancomycin [37]. It is as safe and as well tolerated as standard vancomycin treatment [35]. The search for the ideal antibiotic regime continues, given that recurrence of *C. difficile* colitis after cessation of therapy is common, occurring in 15-30% of patients. One reason for this may be that the antibiotic treatment administered for *C. difficile* colitis does not permit the restoration of the normal bowel flora. Some patients have multiple recurrences. Among non-antibiotics, cholestyramine has been used with dubious results in patients that were unresponsive to antibiotics. The drastic step of total colectomy can only be considered in the context of life-saving surgery for unresponsive ulcerative colitis. Here it is important to operate before life-threatening metabolic changes occur, such as hypoalbuminemia and lactic acidosis, and before the leukocyte count exceeds 16,000 [30].

Probiotics, popular in many fields of gastroenterology, were promoted also as an adjunct to treat *C. difficile* colitis. They consist of preparations of non-pathogenic yeast and bacteria (Lactobacillus GG, Saccharomyces boulardii) in yoghurt or drinks, that are thought to restore the microbial balance of the gastrointestinal tract altered by infection with *C. difficile*. To assess the efficacy of probiotics in the treatment of antibiotic-associated *C. difficile* colitis, Pillai et al examined 3 randomized, prospective studies using probiotics combined with vancomycin or metronidazole for the treatment of documented *C. difficile* colitis, but no benefit was

Table 2 Suggested steps for the prevention and treatment of *C. difficile infections*

Prevention of infection
1. Minimize the frequency and duration of broad-spectrum antimicrobial therapy and the number of antimicrobial agents prescribed, to reduce the risk of *C. difficile* infection [24,47,49].
2. Studies conducted to date provide insufficient evidence for the routine clinical use of probiotics to prevent or treat *C. difficile,* therefore administration of currently used probiotics is not recommended to prevent primary *C. difficile* infection [49,50].
3. Personal disinfection measures include soap and water or chlorhexidine hand-washing (alcohol based hand-rubbing does not kill *C. difficile* spores), use of gloves and gowns [30].
4. Environmental disinfection includes isolation of patients in separate rooms and use of chlorine-containing agents on surfaces and equipment such as telephones, bedrails, floors, stethoscopes, commodes [30,52].
5. Standard procedures for decontamination of colonoscopies are adequate [30].
6. The incubation period is shorter in IBD than non-IBD patients [3]. Initiate stool toxin testing early where *C. difficile* is suspected; do repeat testing if negative.
Treatment
1. Inciting antimicrobial agents must be discontinued as soon as possible [24,51].
2. Antiperistaltic agents should be avoided (may precipitate toxic megacolon).
3. For an initial episode of mild to moderate infection, oral metronidazole is the drug of choice, given as a dosage of 500 mg tid for 10-14 days [24,32,48].
4. For an initial episode of severe infection, oral vancomycin is the drug of choice, given as a dosage of 125 mg qid for 10-14 days. Teicoplanin seems to be as effective as oral vancomycin in treating severe CDI and recurrent CDI, although not available in some countries [24,32].
5. For severe complicated infection, oral vancomycin given as a dosage of 500 mg qid (per rectum if ileus present) with or without intravenous metronidazole 500 mg tid is the regimen of choice.
6. In IBD with *C. difficile* infection, it is controversial whether to stop corticosteroid and immunomodulatory therapy, but biologic agents may be continued [52]. Subtotal colectomy with preservation of the rectum should be considered for severely ill IBD patients [24].
7. A first recurrence of *C. difficile* infection is usually treated with the same regimen used to treat the initial episode, stratified by disease severity [24,32].
8. The preferred treatment for a second or later recurrence of *C. difficile* infection is vancomycin, using a tapered and/or pulse regimen [24,32].
9. Other antibiotics and novel therapies are a last resort.
10. The gastroenterologist should work closely with the specialist in infectious diseases.
11. Consider also other diagnoses if there is no or slow response, such as cytomegalovirus.

found [38]. From these studies there was no firm evidence to recommend probiotic therapy as an adjunct to antibiotic therapy for *C. difficile* colitis.

Another approach to the treatment of *C. difficile* colitis is fecal transplantation [39]. "Fecal transplant" (or "bacteriotherapy") is the nasoduodenal instillation of stool from a healthy donor into the patient, and has been used with a reportedly high success rate in uncontrolled case series [39,40]. Furthermore, a home-based fecal flora infusion did appear to be highly effective and well tolerated in arresting recurrent *C. difficile* [41]. This therapy which presumably breaks the cycle of *C. difficile* is seldom used due to esthetic, cultural and methodological concerns. The value of this method versus vancomycin is being investigated in a trial in the Netherlands.

In another and potentially very promising technique, passive immunotherapy using intravenous immunoglobulins has been shown to be useful for intractable infection in small in uncontrolled case series [42,43]. In 14 patients with severe, recurrent *C. difficile*, on standard therapy but not responding, a single dose of 200-400 mg/kg of IVIG as an additional measure was an effective adjunctive therapy [44]. Very recently, Lowy et al reported a placebo-controlled, multicenter (USA and Canada) phase II trial of 200 patients receiving metronidazole or vancomycin for active *C. difficile* diarrhea, using two fully human monoclononal antibodies against *C. difficile* toxins A and B [45]. These antibodies were studied in the context of reducing *C. difficile* recurrence. It was found that the rate of laboratory-documented recurrent *C. difficile* was 7% in the group receiving the antibodies versus 25% in the controls. The antibodies therapy was also significantly better in patients with the B1/NAP1/027 strain, and in those with previous recurrent infections. The time to response and the duration of hospitalization were not different in the antibody and placebo groups. The majority of recurrences occurred within 30 days; the half-life of the antibody was 22 days. The mechanism of the protective effect of the antibody is as yet unknown, and at this stage it is not likely that antibodies will be used instead of antibiotics as first line treatment. However, they may be useful adjuncts in patients at increased risk for recurrent infection as reported in this study. To be noted, these patients did not have underlying UC or CD. Further prospective controlled studies are warranted to evaluate this therapeutic modality in any event.

Additionally, a vaccine containing *C. difficile* toxins A and B is undergoing clinical trials for prevention of recurrent infection [46]. The use of a nontoxigenic strain of purified *C. difficile* is in early stages of clinical development. A phase I trial of 43 older healthy subjects received 5 days of oral vancomycin, followed by 14 days of nontoxigenic *C. difficile* strain or placebo. The nontoxigenic *C. difficile* strain was well tolerated and detected in stool cultures during and after the dosing period [47].

To summarize, the suggested current guidelines for prevention of *C. difficile* infection and its treatment are given in Table 2. The novel strategies are listed in Table 3.

Table 3 Novel therapies on the horizon

1. Fecal transplant
2. Passive immunotherapy using intravenous immunoglobulins
3. Monoclonal antibodies
4. Nitazoxamide
5. Fidaxomicin
6. Vaccine
7. Intracolonic infusion of a nontoxigenic strain of purified *C. difficile*

Conclusions

C. difficile infection now poses a serious problem in IBD patients. Diagnostic and treatment regimes have gradually improved and some novel therapies such as antibodies, as well as a vaccine, are in the pipeline. Given the changing epidemiology of this infection, the most important step in treating *C. difficile* infection is to maintain an acute awareness of this potential complication in IBD and to act accordingly. The evolvement of exciting new diagnostic and therapeutic modalities is tempered by the absence of definitive evidence for efficacy, so that the initial approach is to apply traditional methods. There is much research to be done still in *C. difficile* infection in IBD patients.

References

1. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996 to 2003. *Emerg Infect Dis* 2006;**12**:409-415.
2. Kelly CP, LaMont JT. *Clostridium difficile* – more difficult than ever. *N Engl J Med* 2008;**359**:1932-1940.
3. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;**5**:339-344.
4. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? *Am J Gastroenterol* 2009;**104**:1298-1313.
5. Ricciardi R, Ogilvie JW Jr, Roberts PL, Marcello PW, Concannon TW, Baxter NN. Epidemiology of Clostridium difficile colitis in hospitalized patients with inflammatory bowel diseases. *Dis Colon Rectum* 2009;**52**:40-45.
6. Sonnenberg A. Similar geographic variations of mortality and hospitalization associated with IBD and Clostridium difficile colitis. *Inflamm Bowel Dis* 2010;**16**:487-493.
7. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;**103**:1543-1450.
8. Lundeen SJ, Otterson MF, Binion DG, Carman ET, Peppard WJ. Clostridium difficile enteritis: an early postoperative complication in inflammatory bowel disease patients after colectomy. *J Gastrointest Surg* 2007;**11**:138-142.
9. Ananthakrishnan AN, McGinley EL, Binion DG. Excess

hospitalization burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Gut* 2008;**57**:205-210.
10. Jodorkovsky D, Young Y, Abreu MT. Clinical outcomes of patients with ulcerative colitis and co-existing Clostridium difficile infection. *Dig Dis Sci* 2010;**55**:415-420.
11. Meyer AM, Ramzan NN, Loftus EV Jr, Heigh RI, Leighton JA. The diagnostic yield of stool pathogen studies during relapses of inflammatory bowel disease. *J Clin Gastroenterol* 2004;**38**:772-775.
12. Butala P, Divino CM. Surgical aspects of fulminant Clostridium difficile colitis. *Amer J Surg* 2010;**200**:131-135.
13. Shen B, Remzi FH, Fazio VW. Fulminant Clostridium difficile-associated pouchitis with a fatal outcome. *Nat Rev Gastroenterol Hepatol* 2009;**6**:492-495.
14. Lundeen SJ, Otterson MF, Binion DG, Carman ET, Peppard WJ. Clostridium difficile enteritis: an early postoperative complication in inflammatory bowel disease patients after colectomy. *J Gastrointest Surg* 2007;**11**:138-142.
15. Kurtz LE, Yang SS, Bank S. Clostridium difficile-associated small bowel enteritis after total proctocolectomy in a Crohn's disease patient. *J Clin Gastroenterol* 2010;**44**:76-77.
16. Tsironi E, Irving PM, Feakins RM, Rampton DS. "Diversion" colitis caused by Clostridium difficile infection: report of a case. *Dis Colon Rectum* 2006;**49**:1074-1077.
17. Morinville V, McDonald J. Clostridium difficile-associated diarrhea in 200 Canadian children. *Can J Gastroenterol* 2005;**19**:497-501.
18. Pascarella F, Martinelli M, Miele E, Del Pezzo M, Roscetto E, Staiano A. Impact of Clostridium difficile infection on pediatric inflammatory bowel disease. *J Pediatr* 2009;**154**:854-858.
19. Kelly PK, Lamont JT. Antibiotic-associated diarrhoea, pseudeomembranous enterocolitis, and Clostridium difficile-associated diarrhea and colitis. In: Feldman M, Friedman LS, Brandt LJ (editors): Sleisenger and Fordtran's Gastrointestinal and liver disease, 9th ed. Saunders: Philadelphia, 2010: 1889-1903.
20. Diggs NG, Surawicz CM. Evolving concepts in Clostridium difficile colitis. *Curr Gastroenterol Rep* 2009;**11**:400-405.
21. Schneeweiss S, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther* 2009;**30**:253-264.
22. Dial S, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. *CMAJ* 2008;**179**:767-772.
23. Nomura K, Fujimoto Y, Yamashita M, et al. Absence of pseudomembranes in Clostridium difficile-associated diarrhea in patients using immunosuppression agents. *Scand J Gastroenterol* 2009;**44**:74-78.
24. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;**31**:431-455.
25. Ticehurst JR, Aird DZ, Dam LM, Borek AP, Hargrove JT, Carroll KC. Effective detection of toxigenic Clostridium difficile by a two-step algorithm including tests for antigen and cytotoxin. *J Clin Microbiol* 2006;**44**:1145-1149.
26. Reller ME, Lema CA, Perl TM, et al. Yield of stool culture with isolate toxin testing versus a two-step algorithm including stool toxin testing for detection of toxigenic Clostridium difficile. *J Clin Microbiol* 2007;**45**:3601-3605.
27. Sloan LM, Duresko BJ, Gustafson DR, Rosenblatt JE. Comparison of real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in diagnosis of Clostridium difficile infection. *J Clin Microbiol* 2008;**46**:1996-2001.
28. Markowitz JE, Brown KA, Mamula P, Drott HR, Piccoli DA, Baldassano RN. Failure of single-toxin assays to detect Clostridium difficile infection in pediatric inflammatory bowel disease. *Am J Gastroenterol* 2001;**96**:2688-2690.
29. Deshpande A, Pasupuleti V, Patel P, et al. Repeated stool testing to diagnose *Clostridium difficile* infection using enzyme immunoassay does not increase diagnostic yield. *Clin Gastroenterol Hepatol* 2011;**9**:665-669.
30. Ananthakrishnan AN. *Clostridium difficile* infection: epidemiology, risk factors and management. *Nat Rev Gastroenterol Hepatol* 2011;**8**:17-26.
31. Balamurugan R, Balaji V, Ramakrishna BS. Estimation of faecal carriage of Clostridium difficile in patients with ulcerative colitis using real time polymerase chain reaction. *Indian J Med Res* 2008;**127**:472-7.
32. Bauer MP, Kuijper EJ, van Dissel JT. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). *Clin Microbiol Infect* 2009;**15**:1067-1079.
33. Nelson R. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. *Cochrane Database Syst Rev* 2007;**18**:CD004610.
34. Musher DM, Logan N, Hamill RJ, Dupont HL, Lentnek A, Gupta A, Rossignol JF. Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006;**43**:421-427.
35. Miller M. Fidaxomicin (OPT-80) for the treatment of Clostridium difficile infection. *Expert Opin Pharmacother* 2010;**11**:1569-1578.
36. Louie TJ, Emery J, Krulicki W, Byrne B, Mah M. OPT-80 eliminates Clostridium difficile and is sparing of bacteroides species during treatment of C. difficile infection. *Antimicrob Agents Chemother* 2009;**53**:261-263.
37. Cornely OA, Miller M, Louie T, Crook D, Sears P, Gorbach SL. Randomized clinical trial (RCT) of fidaxomicin (FDX) versus vancomycin in treatment of recurrent *Clostridium difficile* infection (CDI). 50th Interscience Conference on Antimicrobial Agents and Chemotherapy. Boston, MA, USA. 2010;Abstract L1-1305.
38. Pillai A, Nelson R. Probiotics for treatment of Clostridium difficile-associated colitis in adults. *Cochrane Database Syst Rev* 2008;**23**:CD004611.
39. Aas J, Gesset CE, Bakken JS. Recurrent Clostridium difficile colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. *Clin Infec Dis* 2003;**36**:580-585.
40. Gustafsson A, Lund-Tønnesen S, Berstad A, Midtvedt T, Norin E. Faecal short-chain fatty acids in patients with antibiotic-associated diarrhoea, before and after faecal enema treatment. *Scand J Gastroenterol* 1998;**33**:721-727.
41. Louie TJ, Louie MR, Krulicki W, Byrne B, Ward L. Home-based fecal flora infusion to arrest multiply-recurrent *clostridium difficile* infection (CDI). 48th Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Infectious Diseases Society of America meeting. Washington, DC, USA. 2008; Abstract K-4201.
42. Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea. *J Antimicrob Chemother* 2004;**53**:882-884.
43. Salcedo J, Keates S, Pothoulakis C, et al. Intravenous immunoglobulin therapy for severe Clostridium difficile colitis. *Gut* 1997;**41**:366-370.
44. Yangco BG, Johnson JG. Single Dose Intravenous Immunoglobulin for the Treatment of Severe *Clostridium difficile* Colitis. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy. Boston, MA, USA 2010; Abstract L1-1748.
45. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. *N Engl J Med* 2010; **362**:197-205.
46. Sougioultzis S, Kyne L, Drudy D, et al. Clostridium difficile toxoid vaccine in recurrent C. difficile-associated diarrhea. *Gastroenterology* 2005;**128**:764-70.
47. Villano SA, Tatarowicz W, Seiberling M, Gerding DA, Gomez A, Monnot-Chase E. Phase 1 evaluation of an oral suspension of VP 20621, spores of a non-toxigenic C. difficile strain (NTCD),

in healthy older subjects pretreated with oral vancomycin. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy. Boston, USA. 2010; Abstract F1-2127b.
48. McNulty C, Logan M, Donald IP, Ennis D, Taylor D, Baldwin RN, Bannerjee M, Cartwright KA. Successful control of Clostridium difficile infection in an elderly care unit through use of a restrictive antibiotic policy. *J Antimicrob Chemother* 1997;**40:**707-711.
49. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol* 2003;**24**:699-706.
50. Dendukuri N, Costa V, McGregor M, Brophy JM. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review. *CMAJ* 2005;**173**:167-170.
51. Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med* 2002;**346**:334-349.
52. Navaneethan U, Venkatesh PG, Shen B. *Clostridium difficile* infection and inflammatory bowel disease: understanding the evolving relationship. *World J Gastroenterol* 2010;**16**:4892-4904.