(REVIEW ARTICLE)

Clostridioides (Clostridium) difficile infection: Review of literature

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Abstract

Clostridioides (Clostridium) difficile (*C. difficile*) is a gram-positive bacterium that infects the large intestine. The number of clostridium difficile infections has increased in the recent years due to multiple risk factors including frequent use of antibiotics and proton pump inhibitors. The virulence of *C. difficile* comes from its production of toxins. Treatment for *C. difficile* infection includes the use of antibiotics, monoclonal antibodies, or a fecal transplant.

Keywords: *Clostridioides Difficile*; *Clostridium difficile*; Antibiotics; Toxin; Diagnosis; Treatment; Monoclonal Antibodies

1. Introduction

Clostridioides (Clostridium) difficile (*C. difficile*), also known as the difficult clostridium, was initially identified in 1935 as Bacillus difficilis where it was found in the fecal flora of healthy infants [1]. In 1977, *C. difficile* was identified as the cause of human infections, but it was only found in sporadic cases at that time. In 2000, *C. difficile* became an urgent public health threat due to patients presenting with severe symptoms ultimately causing death [2]. In 2005, the first outbreak from *C. difficile* was officially reported [3].

C. difficile survives in a resistant spore form once outside the colon. These spores are heat, acid, and antibiotic resistant. Once in the intestine, *C. difficile* spores convert to their fully functional vegetative form. These toxins, known as enterotoxin and cytotoxin, are released by *C. difficile* leading to severe inflammation and necrosis of the mucosa [4]. When it comes to the risk of developing an active *C. difficile* infection (CDI), pharmacological agents are known to be the main risk factor. Other factors include a history of diabetes mellitus, inflammatory bowel disease, chronic kidney disease, or cancer. To formally diagnose CDI, the bacteria need to be identified, as well as the genes associated with toxin production, and/or detect the toxin produced by bacteria in watery stool. Treatment of *C. difficile* is very complex and requires an alternating antibiotic regimen depending on the patient's comorbidities, allergies, presentation, and bacterial resistance to antibiotics. Treatment usually involves an infectious disease specialist to closely monitor the patient's clinical course.

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2. Epidemiology

Until 2000, *C. difficile* infection was not a well-known infection, but due to the emergence of a previously rare virulent strain B1/NAP1/027, the incidence of *C. difficile* infection has increased dramatically, making it a global health challenge [5]. It has been estimated that *C. difficile* is responsible for 15-25% of cases of antibiotic associated diarrhea, and all cases of antibiotic-associated pseudomembranous colitis [6]. In terms of individuals who acquire CDI, it is estimated that *C. difficile* causes approximately 500,000 infections annually in the United States, of which 290,000 are hospital associated infections, and 160,000 are community acquired [7]. Up to 4.8 billion dollars are spent each year on treating *C. difficile* infections in U.S. hospitals [8].

Patients over 65 years of age were noted to have a dramatic increase in CDI with double the number of cases for 85-year-olds and above. In 2017, community acquired CDI was also reported in 49% of all CDI cases which is a significantly higher percentage compared to previous years. One of the main factors that lead to the increased CDI in community settings is that *C. difficile* has a highly fluid genome that can modify its content and make it more adaptable to the environment. Community acquired CDI represents a growing public health threat and burden on the health care systems [7]. In addition, there was a decline in the incidence of healthcare associated CDI from 99.6 to 73.3 per 100,000 population primarily driven by a decrease in health care associated infections [9]. An estimated 83,000 patients with CDI have at least one recurrence, and 29,300 patients will die. Up to 25% of patients experience recurrent CDI within 30 days of treatment. Less commonly, recurrent CDI can occur as late as two months after discontinuation of treatment [7].

3. Risk Factors

3.1 Antibiotic use

As mentioned above, the main risk factor for a *C. difficile* infection is the use of pharmacological agents, mainly antibiotics (figure 1). The idea is that antibiotics alter the composition of normal colonic microbial populations, providing a niche for *C. difficile* to flourish and produce toxins. Many antibiotics can cause *C. difficile* infection, but there are few that tend to be frequently associated with the infection such as clindamycin, fluoroquinolones, and cephalosporins.
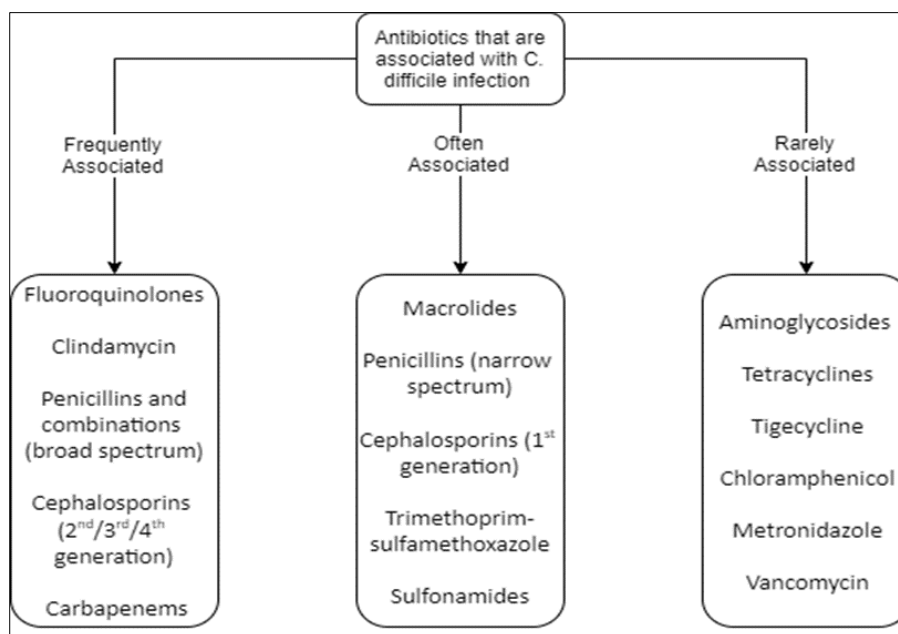
Figure 1 Antibiotics that are associated with *C. difficile* infection

3.2 Advanced age

Advanced age is not only a risk for developing *C. difficile* infection, but these patients are also at an increased risk of morbidity from CDI [10]. An observation study was done in 2002 following the outbreak in Quebec, it was postulated

that persons over 65 years of age were 10-fold higher in frequency at acquiring CDI than younger adults. The reasons behind this association are unclear but may be multifactorial. Host factors of older individuals such as a reduced immune response to CDI, hospitalization, frequent antibiotic use, or inherent dysbiosis may be among the factors that play a role [11].

3.3 Gastric acid suppression

Proton pump inhibitors (PPIs) are widely used in the hospital setting as prophylaxis for gastric ulcer disease. PPIs have been associated with *C. difficile* infection. In fact, *C. difficile* infection has become one of the scariest side effects when it comes to prescribing PPIs. The risk of CDI increases to 1.4 to 2.75 times higher in patients with PPI exposure than with those without PPI exposure, associating gastric acid suppression to an increased risk of CDI [12, 13, 14]. Currently, there are no randomized clinical trials that can state that PPIs cause *C. difficile* infection, but multiple observational studies have shown the association.

3.4 Liver cirrhosis

Patients with liver cirrhosis are at a higher risk of CDI due to recurrent hospitalization visits, frequently administered prophylaxis antimicrobial therapies, chronic PPI use, and immunodeficiency [15]. The use of antibiotics as well as PPIs significantly increase the risk of CDI in healthy populations; therefore, it is expected to increase the risk in cirrhosis patients as well, especially since they are immunodeficient and require frequent hospitalizations. Not only that, but cirrhosis patients are at higher risk of comorbidities and mortality rates from CDI as well.

Other risk factors for acquiring *C. difficile* infection include enteral feeding, gastrointestinal surgery, obesity, cancer chemotherapy, hematopoietic stem cell transplantation, or inflammatory bowel disease [9, 16, 17, 18, 19].

4. Pathogenesis

C. difficile is a spore-forming anaerobe that is found in the intestinal flora. Primary, CDI can be triggered using antibiotics to treat another condition. Additionally, CDI can be a secondary infection by the ingestion of spores from the environment, hence cross-contamination via health-care staff [10]. When in its spore state, *C. difficile* remains dormant, but also resistant to a variety of environmental factors such as heat, acid, and antibiotics. When *C. difficile* is activated by bile acid, it converts to its vegetative state that produces two principal toxins which can cause severe diarrhea and eventually cause life threatening pseudomembranous colitis [20, 21].

The virulence of *C. difficile* comes from its production of toxins. The toxins, Toxin A and B, act on intestinal epithelial and inflammatory cells causing tissue destruction and inflammation. The mechanism behind colonocyte death is through inactivation of the Rho family of guanosine tri-phosphatases which subsequently leads to loss of intestinal barrier function and colitis. Toxin A binds to the brush border of the colonocyte and disrupts the cytoskeleton integrity. This then leads to intestinal fluid secretion and mucosal injury, which causes the patient to have copious amounts of watery diarrhea. Mediators of this pathway include arachidonic acid metabolites, substance P, tumor necrosis factor, IL-8, IL-6, and IL-1. Neutrophils are also directly activated by Toxin A and promote chemotaxis to localize in the pseudo membrane and mucosal layer. Toxin B, found to be cytotoxic, directly destroys enterocyte cytoskeleton structure and causes a pseudomembrane to develop [22].

5. Diagnosis

No single test can accurately diagnose CDI; therefore the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommends a two or three step algorithm consisting of a screening test with high sensitivity followed by a more specific test to detect free toxins (figure 2) [10]. Not every patient presenting with diarrhea should be tested for *C. difficile*. Patients should be tested if they are presenting with acute watery diarrhea (> 3 loose stools) and have associated risk factors such as recent use of antibiotics, recent hospitalization, or are over 65 years old. Liquid stool, noted to be within 24 hours, is the only appropriate specimen for testing [23].

The first test performed to diagnose *C. difficile* is an enzyme immunoassay (EIA) of glutamate dehydrogenase (GDH) antigen test which is a rapid and highly sensitive test. If the test is positive, the following test should be the EIA for Toxin A and B. If one of the toxins is positive, then it is confirmatory for CDI. If the EIA for toxins is negative, but there is still a high suspicion of CDI, it is recommended to obtain a cell culture cytotoxicity assay or nucleic-acid amplification test (NAAT). Both cytotoxicity assay and NAAT are highly sensitive, but cytotoxicity assay takes a long time to run while NAAT can over diagnose CDI by detecting a colonization state. Cell culture is not obtained as a standalone test due to

the inability to confirm whether toxins are present or not. Fecal leukocyte testing is considered to have poor sensitivity when compared to toxin assay and is no longer recommended in the screening for *C. difficile* [24].
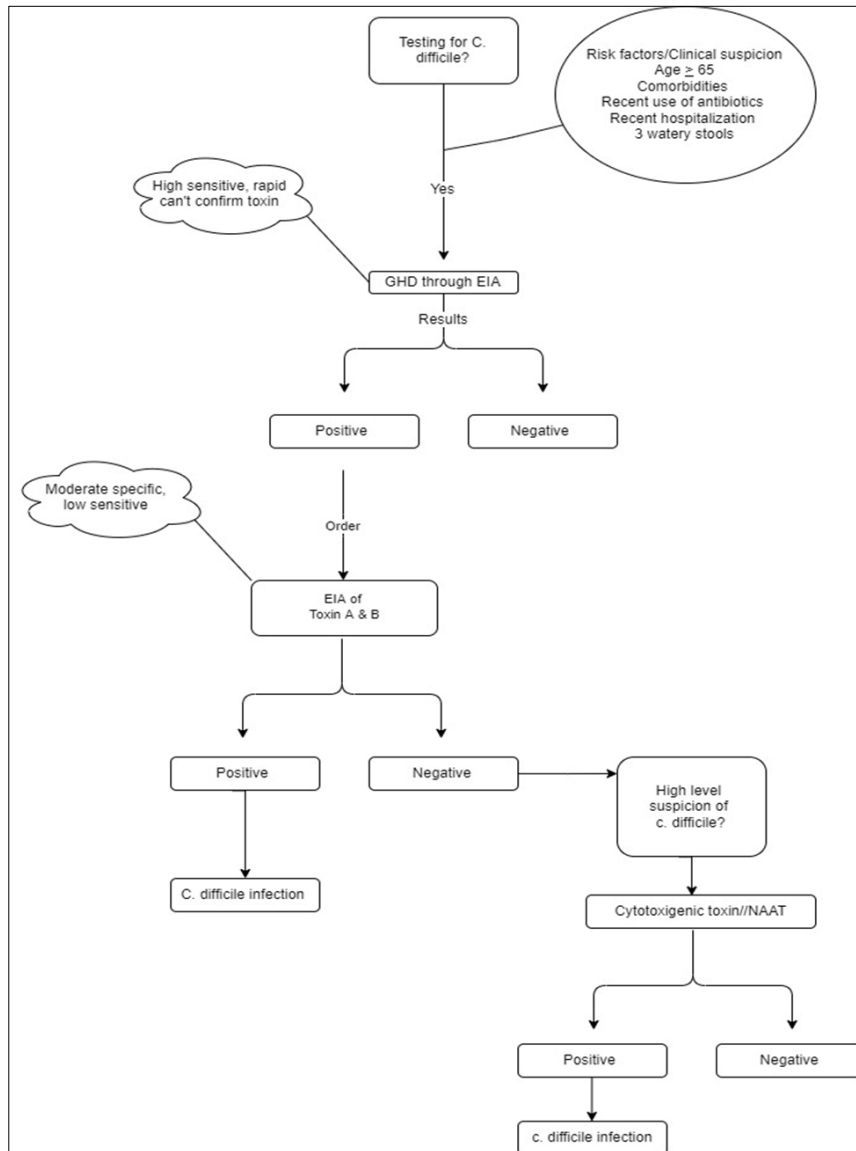
Figure 2 *C. difficile* testing protocol

6. Treatment

Metronidazole and oral vancomycin have been the mainstay of treatment for *C. difficile* infection since the 1970s. However, there have been marked increases in the failure associated with metronidazole, especially in patients with the BI/NAP1/027 strain [23]. Due to the failure of metronidazole, the guidelines for managing *C. difficile* was updated in 2018 with oral metronidazole as no longer the first-line therapy for adults. Currently, fidaxomicin and oral vancomycin are first-line treatments [24]. Choosing which antibiotic is the right treatment for CDI, physicians need to assess the severity of the disease which can be classified into non-fulminant vs fulminant colitis. Non-fulminant can be broken into a non-severe disease which presents with white blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL, while severe disease presents with a white blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL. Fulminant colitis on the other hand presents with shock symptoms such as hypotension as well possible ileus and toxic megacolon.

The main indication for treatment is when a patient presents with acute diarrhea ≥3 loose stools in 24 hours with no other obvious explanation and a positive diagnostic assay. The use of laxatives should be excluded while diagnosing CDI. In addition, if the clinical suspicion is high, treatment can be started empirically while waiting laboratory confirmation.

7. Non-Fulminant Colitis

Following a meta-analysis study that included 22 randomized trails, researchers found that patients presenting with non-severe non-fulminant CDI will benefit from one of the following treatments: oral vancomycin (bacteriostatic): 125 mg every six hours for 10 days or fidaxomicin (bactericidal): 200 mg every 12 hours for 10 days [25]. The recurrence rate of C. diff infection with fidaxomicin has been lower as compared to oral vancomycin with non-NAP1 strain. However, the recurrence rate has been similar with vancomycin and fidaxomicin in NAP1 strain. [26, 27, 28]. For severe non-fulminant *C. difficile* infection, the treatment remains the same as non-severe along with the close monitoring and supportive care of the patients. In addition, surgery should also be consulted.

8. Fulminant Colitis

Surgery consultation along with antibiotics and symptomatic treatment are the mainstay of treatment. Early surgical consultation helps in diagnosing severe disease, who will benefit from surgery, and timely operative management if the condition worsens. The approach to the antibiotics therapy depends on if ileus is present.

8.1 Absence of ileus

Patients with fulminant colitis without ileus can be treated with oral vancomycin 500 mg every six hours in addition to intravenous (IV) metronidazole 500 mg every eight hours. Data regarding the IV metronidazole is limited. A lower mortality rate was observed among the patients who received dual therapy than those that received monotherapy (36% versus 16%) [31, 32].

8.2 Presence of ileus

In patients with fulminant colitis without ileus consideration of addition of vancomycin rectally or fecal microbiota transplant is warranted. However, the risk of colonic perforation is also present with these treatments and therefore should be restricted to the patients who are unresponsive to the standard therapy. If rectal vancomycin is given, it is in addition to the oral vancomycin [32, 33, 34 44-46]. The dosing for rectal vancomycin is not yet established and is often given as a retention enema (500 mg in 100 cc of normal saline every six hours). If recovery is delayed, treatment can be extended up to 14 days from 10 days. In one case series which included nine patients with refractory symptoms, toxic megacolon, or fulminant colitis; eight patients had complete resolution of symptoms and one died from multi-organ failure [32].

9. Indications for Surgical Consultation

- Hypotension with or without use of vasopressors, fever > 38.5 C, ileus, peritonitis, encephalopathy, WBC > 20,000 cells/ml, lactic acid > 2.2, ICU admission, end organ dysfunction, or failure to improve after three to five days of maximum medical therapy.
- Toxic megacolon should be suspected if the patient develops abdominal distension with minimum diarrhea which is due to paralytic ileus resulting from loss of colonic tone.

10. Recurrent CDI

Recurrent *C. difficile* is defined as re-appearance of symptoms within two months after complete resolution of infection after appropriate therapy. The approach to the recurrent *C. difficile* remains the same but varies depending on the number of recurrences.

10.1 Non-fulminant

10.1.1 First recurrence

- If oral Vancomycin was used, treatment needs to be tapered off over six weeks:
- o 125 mg every six hours for 10 to 14 days followed by
- o 125 mg twice daily for seven days followed by
- o 125 mg once daily for seven days followed by
- o 125 mg every two to three days for two weeks
- Alternative: fidaxomicin 200 mg twice daily for 10 days

10.1.2   Second recurrence

Vancomycin pulsed tapered as above or Fidaxomicin 200 mg twice daily for 10 days or Vancomycin 125 mg every six hours for 10 days followed by rifaximin 200 mg every eight hours for 20 days or fecal microbiota transplant.

10.1.3   Third recurrence

Consider fecal microbiota transplant

- Fulminant *C. difficile*: treatment remains the same as that of primary or first episode of CDI.
- Pulse-tapered dosing of vancomycin is believed to facilitate a gradual return of the normal colonic flora. Again, the data on the pulse-tapered regimen is very limited. Vancomycin followed by rifaximin was evaluated in two small studies. In one series, 7 out of 8 patients who were treated had no further recurrence of infection [35].

11. Microbial replacement therapy

It is well understood that antibiotics disrupt the normal flora of the gut which facilitates the proliferation of *C. difficile* and in doing so, the production toxins increase the risk of *C. difficile* infection and recurrence. Due to the alteration of the microbiome, the pathogenesis of *C. difficile* infection has led to the development of the microbial replacement therapies (MRT).

- Nasogastric, nasoduodenal tube, colonoscopy and enema based microbial replacement
- Capsule-based therapies

In a systemic review, which included seven randomized controlled trials and 30 case series, capsule-based therapies proved to be beneficial in 92% of the patient treated with MRT [36]. MRT is administered in multiple ways as mentioned above. A study done in Netherlands showed clinically significant results in 81% of patients after duodenal fecal infusion MRT versus 31% in vancomycin group (However, there is not sufficient data to suggest the use of MRT for treatment of refractory severe CDI. A case series of nine patients showed a resolution of CDI in all the patients with recurrence in one patient who was receiving antibiotics [37]. Currently, there are clinical trials to assess the use of MRT as a primary treatment of moderate to severe CDI or its use before antibiotics.

11.1   Enema based microbial replacement

RBX2660, a microbiota-based suspension derived from donor stool, is being studied in clinical trials for treatment of recurrent CDI (rCDI). Data from phase two trial showed that RBX2660 was superior to placebo with no adverse events. It showed that 51.6 % of patients recovered after the first treatment, and 78.6% who received the second treatment. The overall response was 87.1% [38]. In another phase two study of RBX2660, it met the primary end point of preventing rCDI at eight weeks with success rate of 78.8% compared with 51.8% (p<0.001) in historical control treated with antibiotics alone [39]. Phase three is currently ongoing.

11.2   Capsule-based therapy

SER-109 is an oral capsule that contains spores derived from stool of healthy donors. A study was done in 30 patients with rCDI who were treated with oral antibiotics which showed a resolution of symptoms in 96.7% [40]. The diversity of the gut microbiome increased after SER-109 administration. For example, Bacteroides, a dominant bacterium in healthy populations that is not present in SER-109, increased in 38% of the patients. The prevalence of some pathogens like Klebsiella decreased by 92% by fourth week. Adverse effects of capsule-based therapy include nausea, mild diarrhea, and abdominal pain. However, phase two trials did not show any superiority to the placebo. Phase three trials are currently ongoing. Similar products are CP101, RBX7455, SER-262 and all have ongoing trials.

11.3   Antibody-based therapy

The immune response against the *C. difficile* toxin is an important factor that determines outcomes. The higher the concentration of the antibodies in the serum, the lower the risk of rCDI. Current treatment options include:

- Bezlotoxumab
- Intravenous immunoglobulin

Bezlotoxumab is the first FDA approved human monoclonal antibody which has shown to reduce rCDI in patients 18 years or older receiving antibacterial drug treatment. The mechanism of action is targeted towards Toxin B and neutralizes its effect [41]. Bezlotoxumab is used in conjunction with an antibiotic regimen.

In phase three trials, the use of anti-toxin A was not shown to reduce the likelihood of rCDI [42]. During these trials, cases of heart failure were reported. So, it should be used with caution in patients with history of heart failure if the benefits outweigh the risks. In patients with a history of heart failure, there were more deaths in Bezlotoxumab treated patients 19.5% (n=23/118) than in placebo-treated patients 12.5% (n=13/104). The causes of death varied and included cardiac failure, infections, and respiratory failure [43].

Pooled intravenous immunoglobulin likely has *C. difficile* antitoxin and has been used as an adjunctive therapy in severe and refractory CDI [44]. There is a very limited data available that shows the benefit of IVIG. A retrospective study which included 18 patients with severe CDI who received IVIG in addition to IV metronidazole and/or oral/rectal vancomycin and 61 patients did not receive IVIG therapy. This study showed no significant difference in the study groups regarding mortality or length of stay in the hospital [44].

12. Role of probiotics

Probiotics are the live micro-organisms that are given to restore the gut flora. Many physicians' debate on prescribing probiotics due to lack of objective data stating their benefit. A pilot randomized controlled trial was done which included 33 participants from February 2013 to February 2015. This trial found that probiotic adjunctive therapy was associated with significant improvement in diarrhea outcomes; however, there was no significant difference in the rate of CDI or functional improvement over time between treatment groups [44].

In a meta-analysis which included all the published reports from 1966 to 2007, four studies met the inclusion criteria. One out of these four studies showed a benefit of adding probiotics as adjunctive therapy while the other three showed no significance data [45].

13. Other antimicrobials

There are several other antibiotics that have been used clinically in patients but due to limited data, cost, and questionable outcomes their use is not recommended. These antibiotics are Tigecycline, Teicoplanin, Ramoplanin, Rifaximin, Nitazoxanide, Teicoplanin, Bacitracin, Cadazolid, and Surotomycin.

14. Prevention

Antibiotic stewardship plays one of the most important roles in preventing CDI. Minimizing the use of antibiotics has been shown to decrease CDI [46].

One way to prevent CDI is minimizing use of gastric acid suppression medication. In a meta-analysis which included 7703 patients with CDI, 1525 patients (19.8%) developed rCDI. The rate of rCDI in patients with gastric acid suppression was 22.1% (892 of 4038 patients) compared with 17.3% (633 of 3665) in patients without gastric acid suppression, which indicated an increased risk (odds ratio [OR], 1.52; 95% CI, 1.20-1.94; P < .001) [46].

15. Conclusion

C. difficile infection is infection that results from disruption of normal healthy bacteria in the Colon. It presents with an acute onset of multiple episodes of diarrhea, along with abdominal bloating and fatigue. Patients with *C. difficile* infection should be identified quickly in order to receive the proper treatment. Treatment of *C. difficile* is dependent on patient's presentation. Complication can arise following *C. difficile* infection as well due to medications that are used to treat *C. difficile*, therefore patients with *C. difficile* infection must be monitored closely.

Compliance with ethical standards

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