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Causes, Consequences, and Cures of Clostridium difficile Infection

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Abstract

Clostridium difficile (C. difficile) infection (CDI) is distinctly associated with antibiotic use and the foremost cause of healthcare-associated infective diarrhea. The bacterial spores are primarily transmitted through the fecal-oral route. Worldwide, CDI affects about 8/100,000 individuals each year; the hospitalized population affected is about 4–8/1000 people), causing about 29,000 deaths in the United States alone; and affects about half a million people globally in 2011. In hospital settings, the spores are typically transmitted from the hands of healthcare workers to patients and vice versa. Risk factors for acquiring a C. difficile infection include exposure to most antibiotics, old age (although the younger population can be affected), and immunocompromised or hospitalized patients. The clinical presentation of CDI varies, from asymptomatic carriers to patients with life-threatening colitis. Patients with CDI may present with diarrhea, intense abdominal pain, fever, nausea, weakness, and decreased appetite or anorexia. Although active gastrointestinal bleeding is infrequent, fecal occult blood is positive in specific patients. The most severe form of CDI can lead to dehydration, abdominal distention, hypoalbuminemia, toxic megacolon, colon perforation, intestinal paralysis, kidney failure, septicemia, shock, and death. Most CDI cases are self-limiting with antibiotic therapy withdrawal or vancomycin/fidaxomicin/metronidazole therapy. However, in some patients, CDI can lead to complications requiring surgical intervention. In severe recurrent cases, fecal microbiota transplantation (FMT) is a promising treatment option. The preferred approach concerning CDI is contamination prevention rather than treating active CDI. Regular hand hygiene and other proactive sanitary measures are deemed simple yet effective measures in preventing C. difficile infection.

Keywords: Colitis; Community-Acquired; Enterohemorrhagic; Gastrointestinal; Ileus; Microflora; Nosocomial

Introduction

*Clostridium difficile*, a gram-positive anaerobic spore-forming bacillus, produces specific toxins. The bacterium was officially renamed *Clostridioides difficile* in 2016 [1,2].

Hall and O’Toole (1935) were the first to isolate *C. difficile* from a newborn’s intestinal tract. Until the 1970s, the bacterium was thought to be present, but rarely, in the normal intestinal microbiota. Initially, intestinal infections with *C. difficile* were recognized in patients treated with antibiotics. In a retrospective study, Tedesco., et al. (1974) reported that 21% of the 200 consecutive patients prescribed clindamycin for different indications experienced diarrhea and 10% experienced pseudomembranous colitis [4]. The researchers found that pseudomembranous colitis was often associated with oral administration compared to parenteral administration of clindamycin [4].

At the beginning of the 20th century, the increase in antibiotic use correlated with the rising incidence of *C. difficile* infection (CDI). Currently, CDI is one of the most dreaded nosocomial infections. The bacterial spores are widely distributed in the environment and transmitted through the fecal-oral route. Infected individuals, asymptomatic carriers, and intestinal tracts of animals (such as canines, felines, and avians) act as reservoirs of *C. difficile*. Common repositories of the bacterial spores include lavatories (faucet, toilet seat, and sink basin), furnishings in the hospital ward, phones, and medical equipment (stethoscope, thermometer, and sphygmomanometer). The intestinal tract of 15–70% of infants and 5% of adults are colonized by *C. difficile*. However, the likelihood of intestinal colonization in hospitalized patients is considerably greater [5].

Discussion

Epidemiology

CDI affects about 8/100,000 individuals globally each year [6,7], with an increased burden in the hospitalized population (4–8/1000 people) [6,7]. CDI caused about 29,000 deaths in the United States and affected about half a million people in 2011 [6,7]. Per the Centers for Disease Control and Prevention (CDC), CDI is the most common cause of nosocomial infections in the United States [7].

Risk factors

CDI’s common risk factors include recent exposure to antibiotics, advanced age, increased hospital stay duration, intake of gastric acid-suppressing drugs (such as proton pump inhibitors and H₂ blockers), and underlying illnesses. Exposure to most antibiotics, including those approved for CDI management (e.g., metronidazole and vancomycin), is a risk factor for CDI. Moreover, exposure to extended-spectrum penicillin, cephalosporin, clindamycin, and fluoroquinolone may considerably increase CDI risk [5]. The maximum risk for CDI (i.e., about 8–10 times higher than patients with diarrhea other than CDI) is noted during and about 4 weeks after the antibiotic therapy. However, a significant risk (i.e., about 3 times higher) continues to exist in the subsequent 2 months compared to patients suffering from diarrhea other than CDI [8].

Old age is another crucial risk factor for CDI. The risk is 5–10 times higher in individuals aged > 65 years than those aged < 65 years. Moreover, people aged > 65 years have a greater risk of experiencing CDI and are more prone to experience a severe form of the disease, leading to a higher mortality rate [5,9]. Despite these reports, a significant number of patients with CDI are young.

Recent reports reveal that most CDI infections typically occur in the hospital or nursing home setting (nosocomial). The incidence of community-acquired CDI is also rising, reaching as high as 30% of all the diagnosed CDI cases [10].

The extent of C. difficile colonization among hospitalized patients depends on the geographic location, patient age, and length of hospital stay, varying between 2.1% and 20% [11]. Typically, the bacterial colonization may not always lead to symptoms, with CDI-associated diarrhea occurring in only 25–30% of asymptomatic patients [12].

C. difficile spores can persist in the environment for several weeks or months. The spores are usually transmitted from healthcare workers’ hands to patients and vice versa, highlighting the importance of maintaining regular hand hygiene. Repeated hand hygiene (washing with soap and water) and sterilized gloves can help break the CDI transmission chain [13].

In a controlled clinical trial, Johnson, et al. (1990) investigated the use of vinyl gloves to interrupt C. difficile transmission in hospital settings. The researchers concluded that transmission of the bacterial spores through hands is a primary mode of CDI transmission after finding that the CDI incidence was significantly reduced with vinyl gloves [14].

CDI’s risk is greater in hospitalized patients than those staying in nursing homes; however, nursing home stay also significantly increases CDI’s risk compared to the general population. C. difficile is identified as the most common cause of diarrhea due to nosocomial infections [14].

Suppression of gastric acid could increase CDI development risk [15], although this notion remains to be established through experimental evidence [19]. Further, it has been reported that C. difficile spores are not destroyed by gastric acid [5].

Other less common risk factors for CDI include inflammatory bowel diseases, a recent history of gastrointestinal surgery, an immunosuppressed condition due to underlying malignancy, organ transplantation, chronic diseases (such as chronic kidney disease), and intake of immunosuppressants [5,16].

Pathogenesis

In humans, the normal intestinal microbiota serves as a vital physiological barrier against CDI. The spore form of C. difficile can survive extreme temperature, acidic environment, and antibiotic therapy. On entering the human gastrointestinal tract, the spores germinate mainly under bile acids’ influence [18]. The bile acids, which are byproducts of cholesterol metabolism and produced in the liver, facilitate fat and fat-soluble vitamin absorption from the intestine. In addition to aiding digestion and facilitating gastrointestinal motility, bile acids affect the intestinal microflora [19].

Bile acids are of 2 types: primary and secondary. Primary bile acids (cholic acid and chenodeoxycholic acid) promote germination of C. difficile spores, whereas other members of the intestinal microflora and secondary bile acids prevent germination of C. difficile spores [20]. Moreover, fecal bile acid composition changes in those with CDI. Allegretti, et al. (2016) reported that the stool concentration of secondary bile acids is higher in healthy individuals than in patients with CDI. However, the stool concentration of primary bile acids is significantly higher in patients with repeated episodes of CDI than those with a first CDI episode [21]. The respective stimulatory and inhibitory roles of primary and secondary bile acids on C. difficile spores are involved [22].

Once the balance of intestinal microflora is disturbed, C. difficile begins to colonize the large intestine. Despite the colonization, only a few patients will ultimately develop symptoms [5]. The bacilli are non-invasive, and their virulence is mediated through enzymes, such as

Collagenase, hyaluronidase, and chondroitin-sulfatase, as well as toxins. The enzymes and toxins, together, damage the intestinal epithelial linings, disrupt the tight junctions, and initiate a cascade of local inflammatory changes, such as extravasation of fluid and adhesion of neutrophils. This process leads to impaired function of the intestinal barrier [22,23].

*C. difficile* produces toxins A and B, and certain strains produce *C. difficile* transferase (CDT). Although both toxins are enterotoxic and cytotoxic, toxin A was previously called “enterotoxin A” and toxin B “cytotoxin B”.

After being transported to the cell cytoplasm, the toxins act by inactivating GTPases’ Rho family. The Rho proteins facilitate actin polymerization, thus stabilizing the intracellular cytoskeletal structure. Inactivation of Rho proteins leads to extreme inflammatory responses, resulting in the formation of micro-ulcers with pseudomembranes consisting of dead intestinal cells, neutrophils, and fibrin molecules along the inner lining of the intestine. Lyerly, et al. (1985) conducted an animal study, exploring the effects of intragastric administration of *C. difficile* toxins in various animals. Their findings suggested that toxins A and B act synergistically, and the action of toxin B may occur following tissue damage caused by toxin A [24].

Studies of the action of *C. difficile* in the human colon revealed that the effects of toxins were independent of each other [24,25]. Among all strains of *C. difficile*, the BI/NAP1/027 strain is hypervirulent and resistant to fluoroquinolones. This strain produces a vast number of spores and causes the most aggressive form of the disease. The bacterial strain has two mutations in its toxin regulatory gene tcdC: deletion of an 18 base-pair (bp) and deletion at position 117, which lead to excessive production of toxins A and B [5,26].

The BI/NAP1/027 strain was first identified in the early 21st century in North America and Europe. Before year 2000, the strain was rarely reported. However, in the last decade, the incidence of strain-induced CDI increased multifold, affecting about 51% and 84% of patients in the United States and Canada, respectively [26,27]. Before year 2001, only 14 cases of CDI were caused by BI/NAP1/027, accounting for only 0.2% of all CDI cases [27].

The toxin-induced inflammatory responses lead to the release of cytokines, such as IL-8, IL-1β, IL-6, TNFα, INFγ, and leukotriene B4—which, in turn, are responsible for disease progression [28].

**Clinical manifestation**

The clinical presentation of CDI is varies considerably from asymptomatic carriers to patients with life-threatening colitis. The incubation period of *C. difficile* is uncertain—previous reports specifying 2–3 days and recent reports specifying > 3 days. However, in most cases, the incubation period depends on the affected individual’s health status [29].

CDI can affect all parts of the colon, but the distal segment being most affected. Many patients with CDI present with mild diarrhea, and seem to recover within 5–10 days after antibiotic therapy. However, in some patients, diarrhea might present during antibiotic therapy or a few weeks after stopping the antibiotic therapy.

In addition to diarrhea, patients with CDI can present with intense abdominal pain, fever, nausea, weakness, and appetite loss. Although active bleeding is infrequent, fecal occult blood is positive in individual patients [29].

The most severe CDI form is associated with severe diarrhea, leading to dehydration, abdominal distension, hypoalbuminemia and even shock. CDI’s other life-threatening complications include toxic megacolon, colon perforation, intestinal paralysis, kidney failure, septicemia, and death [29].

In rare cases, extracolonic manifestations (such as reactive arthritis or bacteremia) of CDI have been observed. Although CDI’s mortality rate is about 5%, it increases to 15–25% due to CDI complications. The mortality rate further increases to 34% in patients admitted

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to the intensive care unit (ICU). The mortality rate almost doubles in CDI patients admitted in the ICU than patients admitted to ICU due to other causes [9,30].

Other factors responsible for poor outcomes in CDI include advanced age, leukocytosis, hypoalbuminemia, and increased creatinine level [31]; the Interestingly, the risk of death is increased, especially during the first CDI episode [9].

In many patients, CDI-relapse occurs after the initial episode, even after completing treatment. Despite effective management of the first episode, CDI recurs in 10–25% of patients at least once and in about 65% of patients more than once [32]. It appears that repeat infections with the original strain are the cause of recurrent CDI in half of the cases, whereas repeat infections with different strains are the cause of recurrent CDI in the remaining half. The impaired immune response to C. difficile toxins and re-exposure to spores could also contribute to recurrent CDIs. However, the risk of recurrent infection does not seem affected by antibiotic therapy resistance [33].

Antibiotic resistance plays a notorious role in the emergence of more virulent and recent strains of Clostridium difficile, leading to severe forms of the condition, increased mortality, and a heightened risk of recurrence. Historically, clindamycin resistance led to the emergence of endemic strains of C. difficile; currently, fluoroquinolones resistance is responsible for the emergence of newer types. The newer, more virulent strains are emerging as multi-resistant to specific antibiotics [31–33].

Diagnosis

CDI is first suspected when diarrhea occurs in a hospitalized patient (>3 episodes of stool passage in a day). Diagnosis is confirmed on detecting C. difficile toxins in stool samples. Enzyme immunoassay (EIA) is the most commonly used technique for diagnosing the toxin due to its quick turnaround time of 1–2h, high sensitivity and specificity rates (75–85% and 95–100%, respectively), and cost-effectiveness [15,34].

Alternatively, C. difficile antigens can be detected to confirm the diagnosis. The antigen-detection tests are preferred for their ease of use, quick turnaround time in providing results, and a near-100% specificity. However, the tests are limited in distinguishing toxic from nontoxic C. difficile strains [15,34].

In 2009, the nucleic acid amplification test (NAAT) was introduced. This test has higher sensitivity (80–100%) and specificity (87–99%) than EIA. It is to be noted that the high specificity of the test (95%) very helpful, especially in negative test reports [44,44]. However, NAAT limitations include high cost, difficulty in interpreting the results, and that although the test can confirm the presence of a toxin-producing C. difficile strain it does not readily distinguish the strain’s ability to produce the toxin. Hence, such findings can be misleading in CDI cases where other strains are responsible for causing diarrhea [5,29].

According to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommendations, no single test can be considered a confirmatory test for CDI. Therefore, the best option to confirm CDI is utilizing a combination of two tests. The tests should be chosen such that the first test has a high negative predictive value (EIA/NAAT/antigen test) and the second test has a high positive predictive value (EIAs for toxin A or B). Thus, the second test is performed only if the first test result is positive. However, if the second test result is negative, the patient should be thoroughly evaluated for three possibilities: CDI with low toxin levels, carrier state, and false-negative report. Moreover, a negative antigen test report with a positive toxin test is invalid and should be repeated [35].

Notably, the toxin in the stool samples is unstable and gets lysed after 2h at room temperature. Hence, once collected, the sample should be kept at +4°C and tested within the next 24h [36]. In patients with suspected ileus, rectal swab samples are preferred. Except for epidemiological studies, there are no recommendations for testing asymptomatic patients and repeat testing after completing successful therapy in a patient with previously confirmed CDI [14,37].
Endoscopy assists in evaluating CDI, although it is not recommended in patients with uncomplicated CDI already confirmed through laboratory tests. Endoscopy is preferred in patients with a diagnostic dilemma (with negative C. difficile test reports and no minimal response to standard antibiotic therapy).

Flexible sigmoidoscopy is recommended to avoid injury (perforation) of the already inflamed colon. Colonoscopic findings include the presence of pseudomembranes characterized by elevated white or yellow lesions with irregular distribution and interspersed with normal-looking mucosa. Moreover, the lesions cannot be removed by rinsing. The classical distribution of pseudomembranes may not be present in individual patients with CDI, which does not exclude the presence of infection. The presence of pseudomembranes is rare in patients with recurrent CDI and inflammatory bowel diseases [38].

Other pathological conditions contributing to pseudomembranous colitis include inflammatory bowel disease, Behcet disease, ischemic colitis, collagenous colitis, cytomegalovirus (CMV) infection, and enterohemorrhagic Escherichia coli O157:H7 infection [39].

Radiological investigations are essential for diagnosing complications: the typical finding is the presence of distended bowel loops with wall thickening. Serial ultrasound examination can also be considered for monitoring the width of the inflamed colon [14,40].

Computerized tomography (CT) of the abdomen and pelvis with contrast (oral and intravenous) are used to monitor disease prognosis in patients with severe CDI and evaluate for toxic megacolon and perforated bowel loops. The CT findings assist in surgery decision [41].

Leukocytosis with high C-reactive protein and, in severe cases, hypoalbuminemia suggest the presence of an acute kidney injury [40].

Treatment

Typically, only symptomatic patients are considered for treatment. The presence of C. difficile toxin in asymptomatic patients does not warrant treatment. According to the ESCMID recommendations published in 2014, metronidazole and vancomycin are the mainstay therapies for CDI. Metronidazole is the preferred first-line drug for mild to moderate CDI, whereas vancomycin is considered in severe CDI [42].

Johnson., et al. (2014), in a randomized controlled trial, investigated the effect of vancomycin, metronidazole, or tolevaler in patients with CDI [43]. Data from two identical, phase 3, multicenter, randomized, double-dummy, double-blind RCTs were analyzed. The efficacy of tolevaler was found to be significantly low (the study endpoint included relief from diarrhea and abdominal discomfort for > 2 days after or from day 10 of therapy) compared with both metronidazole and vancomycin (P < 0.001). Further, compared to vancomycin, metronidazole demonstrated an inadequate response (P = 0.02). The primary endpoint was achieved in 81% of vancomycin-treated patients compared to 73% of metronidazole-treated patients. However, in patients with severe CDI, the difference in success following vancomycin therapy (78.5%) was not significantly superior (P = 0.059) to metronidazole therapy (66.3%) [43].

Nelson., et al. (2017) conducted a meta-analysis, investigating antibiotic treatment’s efficacy for C. difficile-associated diarrhea in adults [44]. The efficacy of antibiotics in managing severe CDI cases could not be established as most clinical trials excluded patients with severe CDI. Besides, conclusions regarding the benefits of antibiotic therapy in mild CDI could not be drawn due to the lack of studies with no treatment or placebo-treated groups. There was moderate-quality evidence regarding vancomycin’s superiority to metronidazole and fidaxomicin’s superiority to vancomycin, although the efficacy differences were not considerable. The evidence was slight even for teicoplanin. Thus, the researchers recommended conducting trials comparing cheaper antibiotics, such as metronidazole and teicoplanin [44].

Available since 2011, fidaxomicin is a narrow-spectrum antibiotic primarily effective against gram-positive bacteria, including C. difficile. Trials comparing the efficacy of fidaxomicin and vancomycin in patients revealed comparable or sometimes higher efficacy of the

former. CDI reoccurred in 15% of fidaxomicin-treated patients compared to 25% of vancomycin-treated patients [45]. Similar findings were reported by another study [46]. A meta-analysis also concluded that fidaxomicin could be considered as first-line therapy [47].

In 2017, the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recommended that vancomycin and fidaxomicin should be regarded as the mainstay therapy for CDI [29].

There are no uniform criteria stratifying non-severe and severe CDI. This review defines CDI severity based on other researchers’ generally known risk factors for CDI severity and CDI criteria.

In severe CDI, patients present with or develop ≥ 2 of the following severity markers during the disease course: hypoalbuminemia (serum albumin, < 3 g/dL); white blood cell count, ≥ 15,000 cells/mm³; creatinine, > 1.5 × baselines (or glomerular infiltration rate reduced by 25% from baseline); and temperature, > 38.5°C. In fulminant (severe complicated CDI), patients present with or develop at least one of the following signs or symptoms: admission to an ICU, hypotension with or without the use of vasopressors, ileus, toxic megacolon, mental status changes, serum lactate levels of > 2.2 mmol/L, and evidence of end-organ failure [48].

Even if the ELISA result is negative, empiric antibiotic therapy should be initiated in highly suspected patients. In addition to metronidazole, vancomycin, and fidaxomicin—other antibiotics, such as teicoplanin, tigecycline, bacitracin, and nitazoxanide, can be used. However, these antibiotics are mostly not prescribed and are rarely considered when the first-line antibiotics fail to demonstrate the desired outcome. In pregnant or lactating patients, oral vancomycin is recommended at an appropriate dose [5,49].

Notably, antibiotics other than the standard recommended antibiotics, possibly increase the disease duration and relapse risk. However, when prescribing one of those antibiotics is essential, the treating physician must exercise caution in choosing the appropriate antibiotic. Sulfonamides, tetracyclines, aminoglycosides, or macrolides offer reduced CDI risk and, thus, may also be considered.

**Probiotics**

The exact role of probiotics in CDI remains unclear. Several trials and meta-analyses have advocated the benefits of probiotics in preventing the primary CDI episode. However, these studies had limitations, such as different doses and types of probiotics, strains of *C. difficile*, types of antibiotics, and duration of probiotic therapy [31,50]. Although CDI’s pathophysiology suggests that probiotic therapy may prevent or improve CDI, proper randomized studies are lacking. Thus, it is not prudent to recommend probiotic therapy to prevent or manage CDI at this stage [29].

Asymptomatic *C. difficile* carriers have high levels of antibodies against *C. difficile* toxins, suggesting an important role of immunoglobulins or monoclonal antibodies in the treatment and prevention of CDI relapses, even in first-time attacks [51].

In 2016, bezlotoxumab, a monoclonal antibody binding to *C. difficile* toxin B, was approved by the U.S. Food and Drug Administration to prevent CDI’s recurrence in high-risk patients. In the registration trial, bezlotoxumab and standard oral antibiotics significantly lowered the risk of recurrent infection compared to standard oral antibiotic therapy alone (17% vs. 28%). However, limitations to bezlotoxumab therapy include high cost and a significantly higher risk of heart failure (12.7%) compared to placebo (4.8%) [52].

**Fecal microbiota transplantation (FMT)**

Fecal microbiota transplantation (FMT) is one of the earliest therapies described in Traditional Chinese Medicine during the Dong Lin dynasty (284–364 BCE). FMT was administered to patients with a severe form of diarrhea [53]. In Europe, FMT was first introduced in the 17th century by the Italian anatomist Fabricius Aquapendente [54]. In 1958, Eiseman, et al. used FMT for managing pseudomembranous colitis [55]. The first article on FMT was published in 1983 [56].
Although not yet approved for CDI management, including severe recurrent cases, FMT is an up-and-coming treatment option. In the Netherlands, the use of FMT has been recognized at the national level. The Netherlands Donor Feces Bank (NDFB) has been established at the Leiden University Medical Center. The requests of FMT submitted at the NDFB are evaluated by a group of experts [57]. The procedure yields a high success rate (> 90%), and stringent criteria are used for selecting appropriate patients. Several clinical trials have studied the benefits of FMT and antibiotic withdrawal in CDI management, especially in relapse cases. However, FMT is associated with a high risk of infectious disease transmission from donor to recipient and autoimmune disease development [58].

The majority of the CDI cases are self-limiting upon the withdrawal of antibiotic therapy or with vancomycin/fidaxomicin/metronidazole therapy; however, in some patients, the condition can lead to several complications requiring surgical intervention (e.g., colectomy) [59]. Again, in some patients, the CDI episodes become recurrent; in such cases, FMT seems to help [60].

Prevention

Notably, management strategies to prevent CDI infection must be considered in all suspected cases, not only in confirmed cases. Both healthcare providers and patients’ visitors need to use gloves and gowns during the diarrheal period to prevent C. difficile transmission [61]. Hand hygiene with soap and running water should be strictly followed after every contact with a CDI-patient, and it should be kept in mind that C. difficile spores are not affected or eliminated by alcohol-based sanitizers [62].

Under ideal circumstances, CDI-patients should be isolated and treated in a separate room. If CDI-patient sequestration is not possible, contact—direct and indirect (through the sharing of furniture, books, magazines, and phones) between the CDI-patient and non-CDI-patients or non-CDI-persons—should be strictly restricted [63].

Currently, there are no standardized recommendations for screening asymptomatic C. difficile carriers, even though this measure could interrupt the transmission chain. Hence, it is better to adopt preventive strategies for each suspected or confirmed case. For sanitization of rooms, floors, furniture, and fixtures, chlorine-based disinfectants are highly effective (5000 ppm concentration) [64].

Conclusion

The incidence of CDI has been rising considerably, especially in the hospital setting. CDI can be countered by increasing awareness of transmission routes, hand-washing, glove-use, and proper ward/ICU and device sanitization among healthcare providers. Untreated CDI can lead to severe dehydration, shock, acute kidney injury, and gastrointestinal complications, such as toxic megacolon, ileus, and intestinal perforation. Vancomycin and fidaxomicin are considered first-line drugs for CDI management, with metronidazole being a cheaper alternative. The fecal microbiota transplant is a promising treatment option for C. difficile infections in the future.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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