

Clostridium Difficile-Associated Diarrhea: A Mini-Review

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Abstract

The most common cause of antibiotic-associated diarrhea in hospitals and other health-care facilities is *Clostridium difficile* which is also cause of significant concern because of the increasing morbidity and mortality rates as well as increased health-care costs. The infection by this bacterium was ranging from mild, self-limiting diarrhea to serious diarrhea, pseudomembranous colitis, and life-threatening fulminant colitis which may lead to death. Infection by *C. difficile* develops after ingestion spores of this toxigenic strain by the patients through personal contact or environment. Pathogenicity depending on the production of two types of enterotoxins by bacteria: Tcd A and Tcd B toxins responsible for fluid secretion, inflammation, and tissue necrosis, so identification of this bacterium is depending on the presence of an important virulence factor (enterotoxin) in the stool by using tissue culture cytotoxicity assay, or by enzyme immunoassay for *C. difficile* glutamate dehydrogenase antigen, and sometimes by endoscopy to verify pseudomembranous colitis. The infection can be effectively treated by metronidazole and vancomycin before that, fluids, and electrolytes replacement must be supplied.

Keywords: *Clostridium difficile*, diarrhea, enterotoxins

INTRODUCTION

Clostridia are an important cause of morbidity and mortality in humans and animals. Some of the most common clostridial infections are those of the gut. The primary infections in humans are *Clostridium perfringens* food poisoning and *C. difficile*-mediated antibiotic-associated diarrhea and colitis.^[1]

C. difficile is a Gram-positive, strictly anaerobic, and spore-forming bacteria. In 1935, it was firstly isolated from feces and meconium of asymptomatic newborn infants. Due to its morphology and encountered the difficulties in cultivating it, it was named *Bacillus difficile*. Approximately 10%–35% of all cases of antibiotic-associated diarrhea and the most common infectious cause of nosocomial diarrhea which is associated with substantial morbidity and mortality attributed to infection by these bacteria,^[2] for example, in the United State, the disease has an estimated annual cost of \$ 3.2 billion.^[3] The infection of *C. difficile* is mainly a healthcare associated illness (80%) whereas community-acquired *C. difficile* infection (CDI) (20%) is also of concern.

PATHOGENESIS

After ingestion the spores of a toxigenic strains of *C. difficile* by patient through personal contact or environment, the

infection by these bacteria develops whereas *C. difficile* does not problems among healthy people due to in part commensal bowel flora and antibody-mediated immunity. In the setting of an abnormal or disrupted colonic mucosa, spores of these bacteria colonize the bowel and subsequently germinate to form vegetative bacterial cells which starting to produce two large toxins: An enterotoxin TcdA and a cytotoxin, TcdB. The two toxins are encoded by *tcdA* and *tcdB* genes, respectively. Enterotoxin TcdA primarily acts on intestinal epithelium, leading to cause fluid secretion, inflammation and tissue necrosis, whereas the other one TcdB with its broad cell tropism acts as a potent cytotoxin.^[4] Some strains of *Clostridium* known as NAP1/BI/027 characterized by containing an additional virulence factor (binary toxin) expressed from the *cdtA* (enzymatic component) and *cdtB* (binding component) operon. Until now, it is unknown the extent to which this toxin contributes to the pathogenicity of *C. Difficile*; however, these

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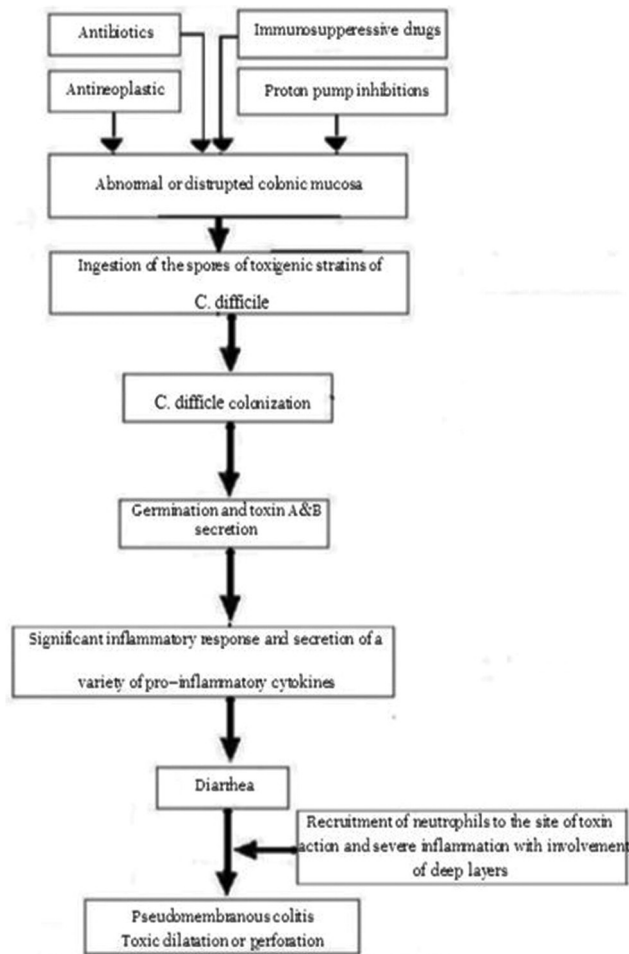


Figure 1: Pathogenesis of *Clostridium difficile* infection^[6]

bacteria were first detected caused severe pseudomembranous colitis, there is no correlation between the severity of disease and the level of fecal toxin [Figure 1].^[5]

EPIDEMIOLOGY

C. difficile is the causative agent of approximately 10%–35% of all cases of antibiotic-associated diarrhea and the most common infectious cause of nosocomial diarrhea, which is associated with substantial morbidity and mortality rates as well as increased health-care costs.^[3]

There is an increasing in the incidence and severity of the disease as the data from different area of the world: Canada, Europe, and the United states disclosed.^[7,8] There are multiple factors responsible for increasing the incidence and severity of the disease including changing demographic situation, increased use of broad-spectrum antibiotics and emergence of hypervirulent *C. difficile* strains known as NAP1/BI/027.^[9,10] This strain is characterized by increased production of toxin A and B, the presence of an additional potential virulence factor (binary toxin) and resistance to newer fluoroquinolone antibiotics, such as moxifloxacin^[11] so this strain was not reported outside Europe and North America, since the late

1990 until 2007, but a survey of period 2008–2010 showed global spread had occurred^[12] as a result of movement of people, animals, vectors, and inanimate objects across international borders.^[10] In different studies, the incidence of CDI varies widely according to the type of hospital care (acute care, long-term) patient population (elderly, young) and the presence or absence of nosocomial outbreaks. For example, prolonged hospitalization and increased number of elderly patients (patients older than 65 years) explain why the incidence of CDI is increased in long-term hospitals. Other study showed that prevalence of *C. difficile* was significantly higher in hospitalized patients versus community patients ($P = 0.0227$).^[13]

CLINICAL FEATURES

A symptomatic carriers vary from 2% in the community to 20%–30% or more in hospitalized adults.^[14] Although asymptomatic, these individuals serves as reservoir for environmental contamination.^[15] The period of incubation between ingestion spore and onset of disease has not be determined. However, most patients develop diarrhea during or shortly after taking antibiotics or up to 8–10 weeks after its decontamination.^[15,16] The infection by *C. difficile* has a wide spectrum range of clinical presentations from mild, self-limiting diarrhea, to serious diarrhea, pseudomembranous colitis, and life-threatening fulminant colitis, which may leading to death. The most important symptom of CDI is watery diarrhea^[17] which is varies from mild, moderate to severe. Patients with colitis (with or without pseudomembranss) usually present with watery diarrhea up to 10–15 times daily, abdominal cramping and pain, fever, anorexia, and nausea so a leukemoid reaction, hypoalbuminemia and occult colonic bleeding may occur, but visible blood is rare.^[18]

DIAGNOSIS

The diagnosis of CDI is basically depend on the clinical features confirmation of the presence of either toxin A alone or both toxins (A and B) together in the stool, and sometimes endoscopy to be sure of pseudomembranous colitis. For those hospitalized patients, who develops diarrhea or any person in the community who develops diarrhea, infection by *C. difficile* should be suspected especially after a course of antibiotics or in association with immunosuppressive therapy. The prevalence of CDI to be 15% in patients with diarrhea.^[13] To confirm infection by *C. difficile*, diagnostic tests are essential, so testing for the bacteria or their toxins must be done only on diarrheal (unformed) stool unless ileus due to *C. difficile* is suspected. Bacterial cytotoxin (toxin B) can be detected by tissue culture cytotoxicity assay in stool filtrate, is considered to be the (gold standard) because it can detect as little as 10 pg of toxin in stool and has a high sensitivity (94%–100%) and specificity (99%–100%).^[19,20]

All strains of *C. difficile* isolates with toxigenic and nontoxigenic are producer to glutamate dehydrogenase (GDH),

C. Difficile (GDH) antigen can be detected by enzyme immunoassay (EIA) which is highly sensitive test (75%–90%) and high negative predictive value (95%–100%).^[20,21] Hence, this test is used for detecting presence of toxin A and toxin B of *C. difficile* in stool. Although this test has reduced sensitivity (65%–85%) it remains the main diagnostic modality and ease of performance because it provides results within (2–6) hours with specificity of (95%–100%).^[19,22] Polymerase chain reaction (PCR) and RT-PCR methods are the diagnostic strategies targeting nucleic acids, they have been developed to detect gene encoding Tcd A and/or Tcd B.^[23] There is another highly sensitive laboratory method for anaerobically isolation of *C. difficile* from stool in culture media, but this method (test) is rarely used for clinical diagnosis because the test required a few days (2–3) to complete and does not differentiate between toxigenic from nontoxigenic strains of these bacteria,^[24] however, this test is important and required for epidemiological studies (i.e., for strain typing in outbreaks of nosocomial infection).^[25] In special situations, such as when other diseases need to be ruled out, the diagnosis is in doubt or the clinical situation required rapid diagnosis, or it is difficult for obtaining a stool sample because ileus develops therefore, Endoscopy is helpful in).^[26,27] To assist the severity of CDI, radiographic imaging studies can be used, computed tomography-scanning also can help categorize the severity of colitis, and it can diagnose fulminant colitis rapidly, so the ascites, free air, colon wall thickening, or dilation can be shown.^[28,29]

TREATMENT

To treat a patient with documented or suspected CDI, the first step includes: Stopping the inciting agent such as antimicrobials, if possible, and providing appropriate supportive care with hydration and electrolyte replacement as needed.^[25] It should be to avoid anti-diarrheal medications as they may obscure symptoms and precipitate toxic megacolon. The mainstays of antimicrobial therapy for CDI are metronidazole and vancomycin.^[14,30,31] In the recommended doses, both of metronidazole and vancomycin have similar efficacy with response rate 90%–97%. Resolution of fever and diarrhea on the 4th or 5th day refers to therapeutic response. The following antibiotics: fidaxomicin, bacitracin, teicoplanin, fusidic acid and nitazoxanide, rifaximin and rifampin, may be considered as alternative therapy for CDI in the unusual events (e.g., allergy or intolerance to both first-line agents).^[32] There are other methods for treatment such intravenous immunoglobulin, specific monoclonal antibodies therapy and toxin-binding agents,^[33] all of them are nonantimicrobial therapies.

PREVENTION

Prevention is best accomplished by implementation of infection-control measures and by judicious use of antibacterial agents.

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Conflicts of interest

There are no conflicts of interest.

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