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Review Article

Clostridium Difficile

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ABSTRACT

Clostridium difficile ; a group of spore forming, toxin forming, gram positive anerobel is implicated in hospital associated diarrhea and is the causative agent of infectious diarrhea. It is the most common hospital associated infection in Europe and North America, and is presumed to be as prevalent in the rest of the world.

There has been emergence of new virulent strain of *C. difficile*, identified as BI, NAP1, and toxinotype III and ribotype 027 (subsequently known as BI/NAP1/027) by various typing method in recent years, implicated in dramatic increase in C. difficile infections.

Diagnosis is established by presence of *C. difficile* toxin or *C. difficile* toxin gene in stool. Lab testing does not distinguish *C. difficile* infection and asymptomatic carriage. Clinical suspicion and positive stool study confirms a diagnosis.

Clostridium Difficile infection, is most common health care associated infection in Europe and North America, and the available studies show it may have similar prevalence in Nepal. Literature review does not reveal any significant study being conducted in Nepal as of now. It warrants further study to exactly determine the incidence/prevalence and its impact in current health care in Nepal. Clinicians need increased awareness and prompt diagnosis to reduce morbidity and further prevention of transmission.

Keywords: Anaerobe; Antibiotics; ELISA; Hypervirulent; Microbiota; Nuclei acid; Pseudomembranes; Toxin

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INTRODUCTION

Clostridium difficile is group of spore forming, toxin forming, gram positive anerobe that is implicated in hospital associated diarrhea and is the causative agent of infectious diarrhea in hospitalized patients. It is the most common hospital associated infection in Europe and North America, and is presumed to be as prevalent in the rest of the world.[1-3] A meta analytical study from 2017 suggest, the prevalence of *Clostridium difficile* infection in Asia to be similar to Europe and North America implicating immediate need of proper clinical and microbiological diagnosis and treatment to further reduce morbidity and mortality. Here we discuss a general idea about the pathogen, risk factors, transmissions, prevention, and current recommendations for treatment.[4]

MICROBIOLOGY, PATHOGENESIS AND EPIDEMIOLOGY

It is an anerobic gram positive bacillus, first described in 1935 in intestine of healthy newborn.[1] It exists in spore forms in an adverse environment and in vegetative form in colonic environment. The spores are resistant to heat, acid, and antibiotics and was found abundant on hospital surfaces (bedding, telephones), on the hands and stethoscopes of health care workers.[5] *Clostridium Difficile* is transmitted by feco-oral route.[6] The organism is non-invasive and colonizes the large intestine. Host intestinal microorganism prevents colonization. The loss of intestinal microorganism with exposure to antibiotics, along with presence of virulent strain and poor host immune response leads to clinical expression of the disease. The organism releases two different types of exo-toxins (TcdA and Tcd B), which subsequently inhibits Rho

family of guanosine triphosphatases (GTPases), causing death of colonocyte, leading to loss of intestinal barrier and neutrophilic colitis.[7]

There has been emergence of new virulent strain of C. difficile, identified as BI, NAP1, and toxinotype III and ribotype 027 (subsequently known as BI/NAP1/027) by various typing method in recent years, implicated in dramatic increase in *C. difficile* infections.[8] This particular strain is characterized by effective spore formation, high toxin production, higher mortality rate, and resistance to fluoroquinolones. This strain is presumed to have a global reach and is found in diverse hospital settings.[9]

C. difficile infection rate in Asia is similar to the rates reported from Europe and North America. Infections from the hypervirulent strain (BI/NAP1/027) were, however, rare as per that study. *C.difficile* infection related mortality was 8.9% in Asia.[4]

Community acquired *C. difficile* infection is defined as disease in an individual who has not stayed overnight in a health care facility within 12 weeks before infection. Disease tends to be of less severity, but the recurrence rates are similar compared to hospital acquired infection. It tends to occur mostly in younger individual and the pathogenesis is not clearly defined as they have not had exposure to antibiotics or have other risk factors.[10]

RISK FACTORS

The most important risk factor is antibiotic use which disrupts fecal microbiota. Other risk factors are advanced age, severe illness, and hospitalizations.[11] Earliest cases were attributed to use of Clindamycin. However, with widespread use of penicillin and fluoroquinolone, it has been associated with use of almost all antibiotics. Some of the antibiotic (e.g., metronidazole) can both incite the disease and provide effective treatment.[13]

Older age (>65 years) has higher risk of contracting the illness. Prevalence is >10 times as high as younger population, for some uncertain etiology. This is presumed to be related to poor host immune response.[13]

The associations between uses of acid suppressive medications/ proton pump inhibitors and *C. difficile* infection remains uncertain. The spores of C. difficile, which are vector of infection, are resistant to acid.[14,15]

Other documented risk factors are presence of inflammatory bowel disease, use of chemotherapy, organ transplantation and immunosuppressive agent, and exposure to carrier or infected individual.[16-18]

DIAGNOSIS

Clinical manifestations

Non severe illness: watery diarrhea is the cardinal symptom. Other associated symptoms are lower abdominal pain/cramps, low grade fever, nausea and vomiting. Stool may contain mucus and blood, but frank hematochezia is rare.[19] Unexplained leukocytosis in hospitalized patient could be related to *C. difficile* infections.[20] Severe *Clostridium Difficile* infection: Described as white blood cell count of >15,000 cells/ml or serum creatinine >1.5 mg/dl. It is associated with hypovolemia, lactic acidosis, fever, sepsis, abdominal distension. Fulminant colitis may present with severe hypotension with multi-organ failure. It can present with ileus and toxic megacolon.[21, 22]

Laboratory evaluation

Diagnosis is established by presence of *C. difficile* toxin or *C. difficile* toxin gene in stool. Lab testing does not distinguish *C. difficile* infection and asymptomatic carriage. Clinical suspicion and positive stool study confirms a diagnosis.[23, 24]

Pseudomembranes can also be seen on radiographic and colonoscopic evaluations. Endoscopic evaluation is not recommended in routine evaluation. It is performed to rule out other underlying pathology. Not all patients with *C. difficile* infection will have pseudomembranes. Presence of pseudomembranes does not confirm a diagnosis of *C. difficile* infection.[25]

C. difficile is currently diagnosed by either enzyme linked immunoassay (EIA) for glutamate dehydrogenase antigen and toxins A and B or by nucleic acid amplification tests (NAATs).[23,24] Enzyme linked immunoassay for GDH: GDH is produced by *C. difficile* isolates and this test has good sensitivity. However, it cannot distinguish between toxigenic and nontoxigenic strains.[26] Enzyme linked immunoassay for toxins A and B: It has relatively high false negative rate, as the organism does not always produce toxin.[28] It has high specificity of 99%, but is 75% sensitive.[27]

Nucleic acid amplification tests (NAATs): DNA based tests, includes polymerase chain reaction. It has very high sensitivity and specificity. Some DNA-based tests also detect BI/NAP1/027 strain. It detects toxigenic strains, but is only recommended to be tested on unformed strain, as it cannot distinguish asymptomatic carriage of toxin producing *C. difficile* strain.[23,24]

Anaerobic culture and cell culture cytotoxic assay: They are resource intensive and time consuming. Culture followed by strain testing for toxin is the Gold Standard for diagnosis if *C. difficile*.[29] Fecal leukocyte testing is not helpful in testing for *C. difficile* infection.[30]

PREVENTION

As *Clostridium difficile* is abundant in health care facilities.
Prevention of initial occurrence: Limited use of antibiotic, prevention of spread of infection in health care facility with proper infection control measures, and use of probiotics. *Clostridium difficile* spores are resistant to alcohol based hand sanitizers. Limit transmission between patients by keeping patient in an isolated room. Health care professionals should wear proper gown and gloves and wash hands with soap and water. Use of probiotic has shown mixed results in prevention of *C. difficile* infection.[31,32]
Secondary prevention; prevention of recurrence: Concomitant use of enteral vancomycin in patient with history of *Clostridium difficile* infection may help reduce the rate of recurrence. Administration of nontoxigenic *C. difficile* strain was associated with lower risk of recurrence some studies.[34]

Bezlotoxumab, a human monoclonal antibody against *C. difficile* toxin B, was associated with substantially lower rate of recurrent

Clinical Definition	Treatment
Non Severe initial episode	Vancomycin 125 mg 4 times daily, by mouth, for 10 days, OR
	Fidaxomicin 200 mg, 2 times daily, by mouth, for 10 days
	Alternative, if above agents are not available, then Metronidazole 500 mg 3 times daily by mouth for 10 days
Severe initial episode	Vancomycin 125 mg 4 times daily, by mouth, for 10 days, OR
	Fidaxomicin 200 mg, 2 times daily, by mouth, for 10 days
Fulminant colitis, initial episode	Vancomycin 500 mg 4 times a day by mouth or by nasogastric tube. If ileus, consider adding rectal vancomycin enemas. Metronidazole 500 mg every 8 hours intravenously, together with oral or rectal vancomycin, particularly if ileus is present.
First recurrence	Vancomycin 125 mg 4 times daily, by mouth, for 10 days if Metronidazole was used in initial episode, OR
	Tapered and Pulsed regimen of vancomycin if standard regimen was used initially, OR
	Fidaxomicin 200 mg, 2 times daily, by mouth, for 10 days if vancomycin was used in initial phase.
Second or Subsequent recurrence	Vancomycin in tapered or pulsed regimen , OR
	Vancomycin 100 mg 4 times daily, by mouth, for 10 days followed by Rifaximin 400 mg 3 times daily, by mouth, for 20 days, OR
	Fidaxomicin 200 mg 2 times daily, by mouth, for 10 days, OR Fecal microbiota transplantation

Adapted from: McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). https://academic.oup.com/cid/article/66/7/e1/4855916

infection among participants receiving antibiotic treatment for primary or recurrent *C. difficile* infection. However, Actoxumab, a monoclonal antibody against *C. difficile* toxin A, did not improve efficacy.[35]

TREATMENT

It is mostly based on type of illness, which is broadly categorized into 3:
Non severe CDI: WBC <15,000 cells/cumm and serum creatinine <1.5 mg /dl
Severe CDI: WBC >15,000 cells/cumm or serum creatinine -1.5 mg/dl
Fulminant colitis: Presence of hypotension, shock or megacolon

Non severe CDI: Oral metronidazole, vancomycin or fidaxomicin have been recommended to use in non severe illness.

Other antibiotics that have activity against *C. difficile* are rifaximin, nitazoxanide, ramoplanin, teicoplanin, and tigecycline.[36,37]

Fecal microbial transplantation: Antibiotic use can cause rapid decline in fecal microbiota and may take up to 12 weeks or longer to recover. The human colonic microbiota is the barrier that prevents *Clostridium difficile* colonization and infection. Fecal microbial transplantation, initially reported in 1958, is emerging modality of treatment in cases of recurrent *C. difficile* infections. The oral or rectal transplantation of the microbiota from tested healthy individual with discontinuation of all antibiotic use was associated with more than 90% success treating recurrent infections.[39-41]

Immunizations

C. difficile toxoid vaccines are in developmental phase. Vaccination against the toxins of *C. difficile* offers the possibility of an effective approach for prevention. Small studies have shown some promising results.

CONCLUSIONS

Clostridium Difficile infection, is most common health care associated infection in Europe and North America, and the available studies show it may have similar prevalence in Nepal. Literature review does not reveal any significant study being conducted in Nepal as of now. It warrants further study to exactly determine the incidence/prevalence and its impact in current health care in Nepal. Clinicians need increased awareness and prompt diagnosis to reduce morbidity and further prevention of transmission.

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