Incidence of *Clostridium Difficile* Associated Diarrhoea in a Tertiary Care Hospital

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**Abstract**

**Background and Objectives**: Rampant and indiscriminate use of broad spectrum antibiotics in hospitalized patients has increased the incidence of *Clostridium difficile* associated diarrhoea (CDAD). Though antibiotic use is the best known risk factor for CDAD, the occurrence of community acquired *C. difficile* suggests the presence of other risk factors too. However CDAD is still under-recognized in India and Asia. Therefore we undertook a prospective study to determine the incidence of *Clostridium difficile* associated diarrhoea in our hospital.

**Methods**: 50 patients of antibiotic associated diarrhoea (AAD) and 50 age and sex matched controls were studied prospectively over a period of 1 year. Controls were patients on antibiotics who did not have diarrhoea. All other causes of diarrhoea were ruled out. Fresh stool samples were examined for the presence of *C. difficile* toxin A and B by the enzyme-linked immunofluorescence assay.

**Results**: 5 patients in the AAD group (10%) and 3 patients in the control group (6%) were positive for *C. difficile* toxin A and B. 5 (10%) patients in the control group showed equivocal results. Out of the 5 CDAD patients, 4 (80%) were males and 1 was a female (p = 2, not significant). 3 patients were from the MICU and 2 were from the medical wards. The median age of the patients was 39 years. Only 1 male patient was > 60 years old (p = 0.781, not significant). All 5 CDAD patients were on proton pump inhibitors (PPIs) and 2 had Ryle’s tube inserted (p = 0.22, not significant). Only 2 patients had leucocytosis (p = 1.67, not significant) and none showed faecal leucocytosis. So out of 100 patients on antibiotics, 8 (8%) tested positive for *C. difficile* toxins in their stools. However, only 5 (3%) had diarrhoea (CDAD) whereas 3 (3%) were asymptomatic carriers.

**Interpretation and Conclusions**: The incidence of CDAD in our hospital was 10% of the 50 patients with AAD. The asymptomatic carriage rate was 6%. All the cases had mild to moderate diarrhoea and were responsive to metronidazole unlike the west where the incidence is higher and the disease more severe.

**Introduction**

Frequent and indiscriminate use of broad spectrum antibiotics has dramatically increased the incidence of *Clostridium difficile* associated diarrhoea (CDAD) in recent years. It is the most common cause of antibiotic associated diarrhoea (AAD) responsible for one-third of AAD cases, 50-75% of antibiotic associated colitis and 90-100% cases of pseudomembranous colitis which is the most severe manifestation of CDAD. CDAD is now considered to be one of the commonest causes of nosocomial diarrhoea. Once considered a nuisance disease, it has lately become a killer disease with the appearance of a hypervirulent strain, toxinotype III in the West. Clindamycin, penicillins, cephalosporins and fluoroquinolones are frequently implicated antibiotics. The prevalence of CDAD is global and the incidence varies considerably from place to place. Additionally, the recognition of community acquired CDAD signals the presence of several risk factors. However, CDAD is still under-recognized in India and Asia.

**Material and Methods**

50 consecutive, hospitalized patients both males and females (25 each) with antibiotic associated diarrhoea were included. 50 age and sex matched controls were also included (Figures 1 and 2). The controls were patients who were on antibiotics but did not have diarrhoea. All the subjects (cases and controls) were selected from the medical, surgical wards and the medical intensive care unit (MICU). All the AAD patients had mild to moderate diarrhoea (passage of 4-5 unformed stools / day not causing hypotension). All the subjects were in the hospital for > 7 days and were on single or multiple antibiotics for > 72 hours for various indications. The antibiotics used were 3rd generation cephalosporins, fluoroquinolones, piperacillin-tazobactam, carbapenems, aminoglycosides, etc. One patient was on clindamycin (Figure 3). Patients with other infective causes of diarrhoea (amoebiasis, cholera, acute gastroenteritis, enteric fever, hepatitis A, E, etc.), HIV and other immunocompromised states, inflammatory bowel disease, irritable bowel syndrome and other chronic diarrhoeas were excluded. All the subjects (cases and controls) were on proton pump inhibitors (PPIs). None of the patients had fever, vomiting, abdominal cramping or bloody diarrhoea. Besides routine investigations, fresh stool sample was sent for routine microscopy and for enzyme immunoassay for both toxin A and B of *C. difficile*. Stool culture for *C. difficile* was not done.

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CDAD is now considered to be the commonest cause of nosocomial diarrhea.\(^1\) Emergence of hypervirulent strains along with indiscriminate use of antimicrobials and inadequate infection control measures in hospitals are the main factors responsible for the recent outbreaks of C. difficile infection.\(^5\) Community associated C. difficile infection (CDI) is being increasingly reported due to the indiscriminate use of H2 receptor antagonists and PPIs.\(^3\) However, CDAD is largely under-recognized in India and Asia, due to the lack of clinical suspicion, difficulty in culturing the organism and cost of the toxin assay.\(^5\) Prevalence of CDAD is around 2-4% in patients without diarrhoea and 7-30% in patients with diarrhoea in different hospital based studies.\(^6-11\) In our study, the prevalence of C. difficile was 10% in hospitalized diarrhoea patients and 6% in non-diarrhoea controls. All the cases and the controls were on antibiotics. Gupta et al\(^6\) isolated C. difficile as a sole pathogen from 7.3% out of 233 patients with acute diarrhoea. Vaishnavi et al\(^9\) reported 30% positivity for C. difficile toxin in hospitalized patients of all age groups receiving single to multiple antibiotics for various diseases, but only in 7% of patients not receiving antibiotics.\(^3\) C. difficile was found to be responsible for 15% of the cases of nosocomial diarrhoea in 1999. Following this study, a stringent surveillance and an improved antibiotic policy was followed and a subsequent study by R Chaudhry from 2001 to 2005 in the same institute showed a decrease in the number of C. difficile positive cases.\(^1\) The predominant risk factor associated with acquisition of C. difficile is antibiotic use in the preceding 2 months, with even a single dose capable of doing the harm.\(^2\) Of late, however the relationship between CDI and antibiotic exposure has been questioned.\(^2\) A recent study of patients with community acquired CDI showed that 61% of patients did not admit to antibiotic exposure within the previous 90 days of developing disease.\(^2\) While all antibiotics have the potential to cause CDAD, certain antibiotics are more notorious in causing the same viz. fluoroquinolones, clindamycin and beta lactam.

### Discussion

CDAD is now considered to be the commonest cause of nosocomial diarrhea.\(^1\) Emergence of hypervirulent strains along with indiscriminate use of antimicrobials and inadequate infection control measures in hospitals are the main factors responsible for the recent outbreaks of C. difficile infection.\(^5\) Community associated C. difficile infection (CDI) is being
agents. Cephalosporins were the most common cause of AAD in our study. Older age and female gender have been identified as risk factors in hospitalized CDAD patients. In our study 4 (80%) out of 5 cases were males and only one patient was > 60 years of age (p=0.781) (Figure 5 and 6). Prolonged courses of antibiotic treatment have been related to an increased risk of AAD. The median time for occurrence of symptoms was 6.46 days after the start of antibiotics in the present study, which was in accordance with other studies. This suggests that disturbance of the normal colonic flora eventually resulting in diarrhoea, takes place within about one week of antibiotic treatment. Prolonged duration of hospital stay has also been reported to be associated with AAD and CDAD. In the present study, the median duration of hospital stay before the start of symptoms was 8 days. PPIs may be a risk factor for CDAD, although conflicting data exist. They are implicated because the survival of spores is facilitated by elevated gastric pH levels and due to the effect of PPI on immune function or on the toxin production of the organism. Until additional data is gathered through clinical studies, clinicians are encouraged to utilize clinical discretion when considering PPI use for their patients. In our study all the AAD cases and the controls were on PPIs.

In the control group, 6% (3/50 patients) tested positive for C. difficile toxins even though they did not have diarrhoea. They were probably asymptomatic carriers whose toxin levels were low and not sufficient to produce symptoms. Also, asymptomatic carriers of C. difficile have been found to have 3 fold higher IgG antitoxin A antibody compared to symptomatic patients rendering them immune. The tests conventionally recommended to diagnose CDAD are stool culture with toxin assay, enzyme immunoassay for toxins and endoscopy where toxin assay is negative but pseudomembranous colitis is strongly suspected. However, stool culture for C. difficile lacks specificity due to the possible faecal carriage of non-toxigenic isolates. Therefore many laboratories rely on toxin detection rather than culture for the diagnosis of C. difficile infection. Besides, a culture would have to be followed by a toxin assay to see if the strain isolated is toxigenic. A European survey of diagnostic methods for C. difficile showed that culture of the organism is performed only in few countries. Mostly C. difficile toxin enzyme immunoassays were used for the diagnosis of CDAD. Enzyme immunoassays for toxin though very specific, lack sensitivity, which can be increased by sending 3 samples. We did not repeat the equivocal assays of our 5 controls due to financial constraints.

### Conclusion

CDAD is a growing nosocomial and public health challenge. Additionally, the recognition of community acquired CDAD signals the presence of other risk factors besides antibiotics. It is still under-recognized in our set-up as the studies are limited, probably due to the lack of technology and facilities for culturing anaerobic pathogens. Prevention of C. difficile infection is challenging. Established guidelines should be followed to minimize exposure to the pathogen which include judicious use of antibiotics, rapid detection of C. difficile by immunoassays for toxin A and B, isolation of patients who have CDAD, proper disinfection of objects and education of staff members. The most successful control measure directed at reduction in symptomatic disease has been antimicrobial restriction.

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### References