SHORT REPORT

Prevalence and clinical course of *Clostridium difficile* infection in a tertiary-care hospital: a retrospective analysis

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Abstract The spectrum of *Clostridium difficile*-associated diarrhea (CDAD) is changing. Apart from antibiotic use, other risk factors such as use of proton pump inhibitors (PPI) and immunosuppressive agents, intensive care unit (ICU) stay and inflammatory bowel disease are being recognized. We retrospectively analyzed data on patients whose stool samples were tested for *C. difficile* toxin (CDT) by enzyme linked immunosorbent assay between June 2006 and May 2008. Demographic and clinical data, and risk factors (antibiotic use, underlying malignancy, chemotherapy, use of PPI, ICU stay) were noted. The details of treatment for CDAD, response, complication and follow up were recorded. Patients whose stool samples were CDT-positive were grouped as study subjects and those with negative stool samples were included in the control group. Of the 99 patients (mean age 46.7 years; 58 men) whose stool samples were tested during this period, 17 (17%) were positive for CDT. As compared with control subjects (*n*=82), study subjects were more likely to have fever, prolonged ICU stay, underlying malignancy, and exposure to immunosuppressive and chemotherapeutic agents. On multivariate analysis, exposure to immunosuppressive agents was the only risk factor associated with CDAD. Fifteen patients were treated with metronidazole and two with vancomycin. Two patients did not respond to metronidazole but responded to vancomycin. No patient developed any complication. The prevalence of *C. difficile* toxin in diarrheal stools sent for *C. difficile* toxin testing was 17%. Exposure to immunosuppressive agents was a risk factor for the infection. Metronidazole was effective in a majority of patients.

Keywords Antibiotic-associated diarrhea ·
Immunosuppressive agents · Proton pump inhibitors

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Introduction

Diarrhea is common in hospitalized patients, especially in those who receive antibiotics with incidence ranging from 3% to 29% [1]. *Clostridium difficile* is the most commonly identified organism as the causal agent for antibiotic associated diarrhea [2]. Because of the frequent use of broad-spectrum antibiotics, the incidence of *C. difficile*-associated diarrhea (CDAD) has risen dramatically in recent years, especially in North America and Europe [3, 4]. In addition to recognized risk factors, like old age, hospital admission, and antibiotic exposure, there have been recent reports of the occurrence of CDAD in young seemingly healthy adults and children in the community, some without antimicrobial exposure [5, 6]. Immunocompromised state is also recognized as a risk factor for CDAD [7–11]. Acid suppression, especially with proton pump inhibitors (PPI), has been reported in a number of studies to be associated with an increased risk of *C. difficile* infection [12]. *C.*

difficile has been implicated as a cause of exacerbation in patients with inflammatory bowel disease [13–16]. Most studies on the prevalence and morbidity of *C. difficile* are from the Western countries. Data from India are limited to a few studies [17–22]. This study was done to study the profile of *C. difficile* infection in our tertiary-care center.

Methods

This was a retrospective study of all in-patients as well as out-patients attending our hospital, from June 2006 to May 2008, and whose fecal specimens were sent to the laboratory for *C. difficile* toxin testing. Ninety-nine such specimens from patients with diarrhea were sent. The hospital records of the corresponding patients were retrieved and clinical data were noted. Demographic and clinical data including age, sex, duration of hospitalization and ICU stay of in-patients, duration of diarrhea, clinical features, associated and/or underlying illnesses (inflammatory bowel disease, prior abdominal surgery, malignancy, prior hospitalization, immunosuppressive state), and addictions were recorded. Exposure to antibiotics, immunosuppressive agents, cancer chemotherapy, and PPI was noted. Details of any procedures done, if any, were noted. Sigmoidoscopic or colonoscopic findings and histopathology report, whenever done, were included. Data in patients with *C. difficile* infection (study group) were compared with those in patients without (control group).

Testing for toxin A and toxin B of *C. difficile* was performed on the stool samples using an enzyme-linked immunosorbent assay (Ridascreen Kit, Darmstadt, Germany) according to the manufacturer's instructions.

Details of treatment given to patients with positive stool samples were recorded. The drug, duration and response, clinical course, and follow up of these patients were noted.

Statistical methods

Stata SE version 10.1 (StataCorp LP, Texas, USA) was used to analyze data. Student's t test for unpaired data was used for comparing means and Chi-square test or Fisher's exact test (as appropriate) for comparing proportions. To examine the relationship of each independent variable with the dependent variable, binary logistic regression was performed. Entry into the analysis was *p*-value of <0.1 in a univariate analysis. *T*-test was performed for age and duration of illness. A *p*-value of <0.05 was deemed statistically significant.

Results

Ninety-nine stool samples were tested for *C. difficile* toxin assay during the study period. The year-wise breakup was

2006 = 21, 2007 = 28, and 2008 = 50. Each patient's stool was tested only once. The mean age of the patients whose samples were analyzed was 46.7 years and 58 (58%) were men. Four patients were below 2 years of age.

Stool positivity for *C. difficile* toxin assay

Seventeen (17%) stool samples were positive for both *C. difficile* toxin assay A and B. Of these, only one positive sample belonged to a one-year-old infant. There was no difference in the age, gender distribution, and clinical features except fever, prior hospitalization, presence of inflammatory bowel disease, previous GI surgery, or antibiotic use between the two groups (Table 1). Compared with the control group, study subjects were more likely to have fever, underlying malignancy, prolonged ICU stay, and exposure to immunosuppressive and chemotherapeutic agents (Table 1). On multivariate analysis, exposure to immunosuppressive agents was the only significant associated variable (Table 2).

Clinical course and treatment

The median duration of diarrhea in the study patients was similar to that in the control group (5 vs. 7 days). None of the patients developed any complication and there was no mortality. Fifteen study patients were treated with metronidazole; two were given vancomycin as the first drug. The median duration of treatment was 7.5 (5–14) days and the median time taken for resolution of diarrhea was 3 (2–10) days. Two of the 15 patients treated with metronidazole did not respond and were subsequently treated with oral vancomycin, to which they responded.

Discussion

Most previous studies about CDAD in India have shown prevalence rates ranging from 7.1% to 26.6% [17–22]. Three prospective studies in hospitalized patients developing acute diarrhea showed prevalence rates of 11.1%, 22.6%, and 26.6% [17, 21, 22]. A recent retrospective study by Chaudhry et al. on hospitalized patients, found the prevalence over a five-year period to be 7.1% [19]. We found a prevalence rate of 17% in a combined cohort of in-patients as well as out-patients.

CDAD has been reported to be more common in women and older patients [23]. The mean age of patients with CDAD in our study was 45.2 years and there were more men (64%). Studies from India have reported varying male-female ratios [19, 24–26]. Among patients positive for *C. difficile* toxin, fever, cramping abdominal pain, and diarrhea have been reported to be more common [4, 27]. In our

Table 1 Demographic and clinical data of the patients

	Total (n=99)	Study patients (n=17)	Control group (n=82)	Odds ratio (95% CI)	p-value
Men	58 (58)	11 (64)	47 (57.3)	–	0.39
Age (years) (mean [SD])	46.7 (21.4)	45.2 (23.4)	47 (21.1)	–	0.76
Duration of diarrhea (days) (median [range])	7 (1–120)	5 (2–30)	7 (1–120)	–	0.22
Clinical features and risk factors					
Smoking	7 (7)	2 (11.7)	5 (6.09)	2.05 (0.17–13.9)	0.35
Alcohol	6 (6)	1 (5.88)	5 (6.1)	0.96 (0.01–9.49)	1.00
Fever	27 (25)	8 (47)	19 (23)	2.94 (0.85–9.9)	0.07
Abdominal pain	31 (31)	7 (41.1)	24 (29.2)	1.7 (0.48–5.5)	0.33
Hematochezia	9 (9.09)	3 (17.65)	6 (7.32)	2.7 (0.38–14.4)	0.18
Inflammatory bowel disease	14 (14.1)	3 (17.65)	11 (13.4)	1.38 (0.21–6.21)	0.70
Previous GI surgery	3 (3.03)	0 (0)	3 (3.66)	–	1.0
Malignancy	16 (16.1)	6 (35.29)	10 (12.2)	3.92 (0.96–14.82)	0.03
Organ transplant	1 (1.01)	1 (5.88)	0 (0)	–	0.17
Prior hospital stay	45 (45.5)	9 (52.94)	36 (43.9)	1.43 (0.44–4.74)	0.5
Intensive care stay	17 (17.2)	7 (41.18)	10 (12.2)	5.04 (1.29–18.6)	0.009
Antibiotic use	37 (37.4)	8 (47.06)	29 (35.4)	1.62 (0.48–5.3)	0.364
Immunosuppressive therapy	24 (24.2)	9 (52.94)	15 (18.3)	5.03 (1.42–17.5)	0.005
Proton pump inhibitors	23 (23.2)	7 (41.18)	16 (19.5)	2.88 (0.8–9.8)	0.065
Chemotherapy	7 (7.07)	4 (23.53)	3 (3.66)	8.10 (1.18–59.8)	0.016

Data are as n (%)

patients, though fever was more common, there was no difference in the occurrence of abdominal pain and duration of diarrhea.

C. difficile should be considered as a cause of diarrhea in high-risk patients even if the classical features not present. Fulminant colitis leading to ileus, toxic megacolon, perforation, and death have been reported in 1% to 3% of cases [28]. None of these complications was found in our study group. There was no mortality in our patients. Similar results have been shown from other studies [19, 26]. In a retrospective study over 5 years, 8 of 37 *C. difficile*-positive patients died, but the cause of death was not directly related to *C. difficile* diarrhea [19]. Similarly, Gogate et al. reported the death of two of their patients with *C. difficile* infection, one died from renal failure and the other was a case of hepatoblastoma [26].

Antibiotic usage is a common cause of diarrhea and these drugs have been implicated as an important risk factor for CDAD [29]. However, in our study, *C. difficile* positivity was not influenced by prior antibiotic use. Vaishnavi et al. reported that antibiotic usage was not different in adults with or without *C. difficile* toxin [30]. Studies have shown that ICU stay, underlying diseases, like malignancy and inflammatory bowel disease and exposure to chemotherapy, immunosuppressive, and PPI are additional risk factors [3, 4, 13, 14, 31, 32]. We found that underlying malignancy, ICU stay, and exposure to immunosuppressive and chemotherapeutic agents were associated with *C. difficile* toxin positivity on univariate analysis; however, only exposure to immunosuppressive agents was a significant risk factor on multivariate analysis. Kumar et al. reported that patients with psoriasis receiving methotrexate and/or mesalazine had increased prevalence of

Table 2 Logistic regression multivariate analysis of factors associated with *C. difficile* infection

Factors	Adjusted odds ratio (95% CI)	p-value
Fever	4.32 (1.16–16.05)	0.028
Malignancy	3.65 (0.66–20.05)	0.136
Intensive care stay	4.04 (0.95–17.08)	0.058
Immunosuppressive therapy	5.38 (1.43–20.15)	0.012
Proton pump inhibitors	1.84 (0.45–7.45)	0.389
Chemotherapy	2.38 (0.24–22.51)	0.462

C. difficile toxin [33]. In our study, corticosteroids were responsible for all of the cases with *C. difficile* toxin positivity.

Vancomycin has been shown to be superior to metronidazole in the treatment of severe CDAD [34, 35]. In our study, 13 of 15 patients treated with metronidazole responded; two who did not respond to metronidazole responded to vancomycin. Zar et al. found that the efficacy of metronidazole was comparable to that of vancomycin [34]. The cost difference between metronidazole and vancomycin is an important consideration. The clinical practice guidelines update by the Society of Healthcare Epidemiology of America and Infectious Diseases Society of America suggest that metronidazole be the drug of choice for the initial episode of mild to moderate *C. difficile* infection, and vancomycin be used for initial episode of severe *C. difficile* infection [36].

There is increasing evidence of increased susceptibility of patients with IBD, especially those with ulcerative colitis, to *C. difficile* infection [13, 14]. Balamurugan et al. found increased fecal carriage of *C. difficile* in patients with ulcerative colitis as compared to healthy individuals [16]. No such difference was found in our study, but the number of patients was small.

Our study had several limitations. It was a retrospective analysis of data based on stool samples sent to the laboratory specifically for this test. The clinical suspicion of infection was possibly high, leading to a selection bias from among all patients with acute diarrhea. The number of patients in each risk group was small with possibility of a type 2 error.

To summarize, the prevalence of *C. difficile* toxin in diarrheal stools sent for *C. difficile* toxin testing was 17%. Exposure to immunosuppressive agents was a risk factor for the infection. There was no notable feature except fever in the clinical presentation. Metronidazole was effective in a majority of patients.

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