Original Article

Clinical Profile of Clostridium Difficile Associated Diarrhea: A study from Tertiary Care Centre of South India

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ABSTRACT

Background: Clostridium difficile infection (CDI) is a common cause of diarrhea in hospitalized patients worldwide however it is uncommonly reported from Indian hospitals and clinical profile of Indian patients with CDI is not well studied.

Methods: This was a retrospective study done in a tertiary care centre of South India between March 2016 and May 2017. Case records of all patients for whom stool samples were sent for either C. difficile toxin assay or GeneXpert C. difficile were analysed. Coloured immunoassay (CerTech) was used for detecting Glutamate dehydrogenase (GDH) and Toxin A and B and nucleic acid amplification assay (Xpert, Cepheid) were used.

Results: A total of 112 were analyzed, out of which 18 were positive and negative cases (n = 94) were taken as controls. Prevalence of CDI was 16%. Presence of fever (OR = 8.5), tenesmus (OR = 8.5), hematochezia (OR = 4.5), cramps (OR = 8.27), use of immunosuppressive agents (OR = 3.62) and duration of antibiotics (7.38±6.50 vs 4.54±6.57 days; p=0.019) was significantly higher among cases.

Conclusion: Although the prevalence of CDI is low in India compared to the west, it still contributes to significant morbidity in hospitalized patients as it is responsible for more than 1 in 6 cases of diarrhea in hospitalized patients. Fever, cramps, tenesmus, hematochezia, use of immunosuppressants and antibiotic therapy of more than 7 days suggest a diagnosis of CDI, and should trigger testing and treatment. Outcomes are good with appropriate therapy.

KEYWORDS: Clostridium Difficile; Diarrhea; Antibiotic associated diarrhea.

Introduction

Diarrhea is a common symptom in hospitalized patients, causes ranging from drugs given to the patient to the underlying disease per se.[1,2] Clostridium difficile infection (CDI) is a common cause of nosocomial diarrhea worldwide, and leads to increased health care expenditure, morbidity and mortality.[3,4] The infection causes an estimated 3000 deaths every year in the UK and 15000-20 000 deaths in the USA[5,6] with associated case-fatality rates of 6-17%.[7-10] Over 250,000 people need hospital care and at least 14,000 people die from CDI in the United States each year based on statistics from the Centers of Disease Control and Prevention.[11] However, there are few single centre studies from India, which describe prevalence of CDI among hospitalized patients ranging from 4% to 21%.[12-14] It is possible that CDI is an under estimated disease in Indian hospitals.

Risk factors for CDI are antibiotic exposure, prolonged hospital stay, immunocompromised state, use of PPI, GI surgery and exposure to anti-neoplastic drugs.[15-18] To the best of our knowledge these classical risk factors of CDI have not been well studied in Indian hospitals except for a study done by Ingle et al which found that presence of fever, malignancy, ICU stay, exposure to PPI, chemotherapy and immunosuppressive therapy was associated with CDI.[19]

Data from India on the prevalence, risk factors and morbidity of C. difficile are limited to few studies.[12,20,21] This study was done to understand the epidemiological and clinical profile of hospitalized patients with C. difficile infection.

Methods

This was a retrospective study on inpatients admitted to a tertiary care 550 bed hospital between March 2016 and May 2017. Case records of patients whose fecal specimens were sent to the laboratory for identification of C difficile by immunoassay and/or PCR were analyzed. Each patient's stool was tested only once. Demographic and clinical data including age, sex, clinical symptoms (frequency of stools, abdominal cramps, tenesmus, fever and other important relevant symptoms), history of prior antibiotic exposure, reason for admission, history of use of anti-neoplatic drugs, PPI exposure, surgery, presence of other co-morbidities (especially IBD), history of smoking or alcohol, hemodynamic parameters, diagnostic modality used by the clinician to diagnose C. difficile infection, treatment given if CDI was confirmed and duration of treatment were noted. Sigmoidoscopic or colonoscopic and histopathological findings, whenever done, were included.

Patients whose stool samples were positive for toxin assay and/or for PCR were taken as cases and those whose stool samples were negative were taken as controls. Intergroup analysis of various epidemiological and clinical factors was done. Patients with < 18 years of age and who had some other established cause of diarrhea were excluded.

Testing for GDH and toxin of C. difficile was performed on the stool samples using either

1. A chromatographic immunoassay by Certest Clostridium difficile GDH + Toxin A+B (combo card test) for simultaneous qualitative detection
2. Xpert C. difficile Assay, performed on the Cepheid GeneXpert Systems according to the manufacturer's instructions.

Various study parameters were recorded in Microsoft Excel 2010 and statistical analysis was done using SPSS software 23.

Results

We identified 124 such case records over the study period, out of which 12 case records were of outpatients and were excluded from the study. Hence a total of 112 case records were analyzed of whom 18 were positive, leading to a prevalence of CDI of 16%. Seventy eight stool samples were tested by C. difficile toxin assay, 58 by Xpert C. difficile assay and 23 had both the tests done during the study period of the 18 patients included as cases (group A), 15 were positive for toxin assay among which one also had pseudomembrane and one also was PCR positive, 2 had pseudomembranous colitis with negative toxin assay and one had only PCR positive. The remaining 94 were negative for either toxin assay, PCR or presence of pseudomembranes and served as controls (group B).

The mean age of the patients among group A was 52.16 ±14.13 years and among group B was 53.87±16.12 years which was comparable. Fifty five percent were males in group A and 60.5 % were males in group B which was comparable.

Among the symptom analysis, duration (4±6.68 days vs 4.73±8.41 days, p=0.68) and median frequency of diarrhea (7 vs 5, p=0.06) were not significantly different in intergroup analysis **[Table1]**. Compared with the control group, study subjects had significantly higher incidence of fever (OR:8.5, p=0.0001), cramps (OR:8.27, p=0.001), hematochezia (OR:4.5, p=0.02) and tenesmus (OR:8.5, p=0.0001) **[Figure1]**. No patient had CDI relapse although follow up was limited to time of hospital discharge.

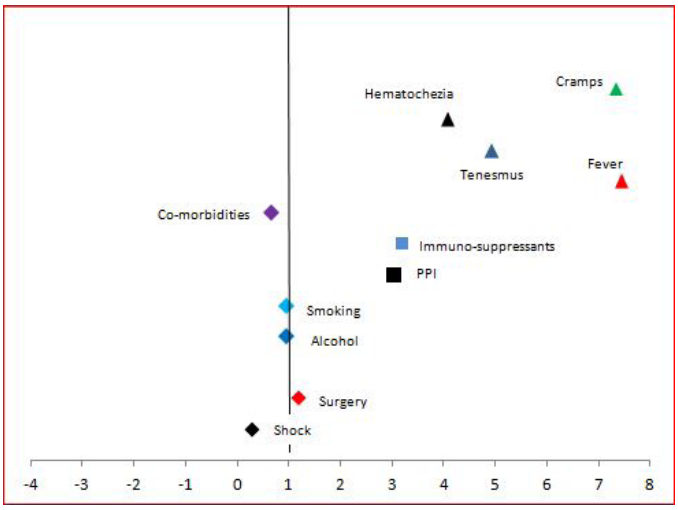

Figure 1: Forest plot showing distribution of odds ratios.

Table 1 : Comparison of various clinical and biochemical features of case and control groups.

Characteristics	Study patients(n-18)	Control group(n-94)	Odds ratio	p-value
Age (n)	52.16 ±14.13	53.87±16.12		0.65
Male (n)	10	57	0.811	0.6
Symptoms				
Frequency of diarrhea	7 (3-20)	5 (2-20)		0.06
Duration (days)	4±6.68	4.73±8.41		0.68
Cramps (n)	11	15	8.27	0.001
Hematochezia (n)	3	4	4.5	0.02
Tenesmus (n)	1	1	5.47	0.0001
Fever (n)	13	22	8.5	0.0001
Risk factors				
Comorbidities (n)	12	64	0.93	0.9
Immunosuppressants(n)	8	17	3.62	0.013
PPI (n)	11	29	3.52	0.014
Duration of Antibiotics (days)	7.38±6.50	4.54±6.57		0.019
Smoking (n)	1	9	0.55	0.58
Alcohol (n)	2	8	0.714	0.72
Surgery				
GI (n)	2	8	1.2	0.72
Non GI(n)	2	8	2.21	0.67
Shock (n)	1	14	0.33	0.28
WBC count (µL)	11303±8594	8,771±3985		0.23
Creatinine (mg/dL)	1.53±0.68	1.37±1.11		0.41

Among the risk factors which are associated with CDI, presence of co-morbidities (OR:0.93, p=0.9), surgery (OR:1.2, p=0.72) and smoking (OR:0.55, p=0.58) were not found to be statistically significant between the two groups. However, exposure to PPI (OR:3.52, p=0.014), immunosuppressants (OR:3.62, p=0.013) and duration of antibiotics (7.38±6.50 vs 4.54±6.57 days; p=0.019) were significantly associated with development of CDI [Figure1].

Factors which assess severity of CDI like shock (OR:0.33, p=0.28), WBC count (11303±8594 vs 8,771±3985 cells/µL, p=0.23) and creatinine (1.53±0.68 vs 1.37±1.11 mg/dL, p=0.41) were comparable.

Ten study patients were treated with metronidazole; eight were given vancomycin as the first drug. The median duration of treatment was 8.55±1.72 days. None of the patients developed any complication and there was no mortality.

Discussion

Diarrhea in hospitalized patients leads to increased length of stay and health expenditure. Causes of nosocomial diarrhea include noninfectious agents like drugs, underlying illness and enteral feeding; and infectious agents like C. difficile, norovirus and toxigenic strains of Clostridium perfringens, Klebsiella oxytoca, Staphylococcus aureus, and Bacteroides fragilis 2. C. difficile is now widely recognized cause of nosocomial diarrhea affecting 1% of hospitalized patients 22. CDI leads to an annual cost of $1.0 to $4.9 billion to the US healthcare system.[23] Fortunately, CDI has not been implicated as much in India but it could be possible that it is under-recognized. In a recent meta analysis, it was shown that incidence of CDI was 5.3 per 10,000 patients days from Asian countries which was similar to western countries.[24] This meta-analysis also included few Indian studies highlighting the fact that CDI has been under recognised in Indian settings. Most recent studies on C.difficile in India have shown prevalence rates ranging from 4% to 21%.[13,14,21] A prospective study in hospitalized patients developing acute diarrhea showed prevalence rates of 26.6%.[21] We found a prevalence of 16% similar to the above studies.

C. difficile forms endospores and survives for a long duration in the external environment leading to increased transmission in health care settings and difficulty in eradication. Increased gastrointestinal tract colonization may lead to toxigenic C difficile infection. Depletion of gut flora allows endogenous or environmental C. difficile to proliferate in the colon and produce toxin A, toxin B or binary toxin, which is seen in hypervirulent strains (NAP-1) and associated with severe infections.[25] C. difficile causes a range of effects, including gut mucosal damage which in turn may lead to asymptomatic carriage to fulminant colitis. CDI occurs particularly during the use of the antibiotic and within the first month after antibiotic use, but the risk persists for up to 90 days.[26] Since the features of health-care-associated diarrhea cannot reliably distinguish CDI from other causes, laboratory confirmation is essential.

After clinical suspicion of CDI, diagnosis is confirmed with microbiological evidence of toxin-producing C. difficile in stools, or colonoscopic or histopathological findings of pseudomembranous colitis (PMC). Toxin A+B EIAs were most widely used diagnostic tests but they have low sensitivities.[27] There are various methods to detect toxin A and B which include EIA, latex agglutination and ELISA with sensitivities ranging from 75%-95% and specificity from 83%-98%.[27] We used a chromatographic immunoassay by Certest to detect GDH and Toxin A and B. This test has claimed sensitivity and specificity of >99 % in comparison with C difficile QUIK CHEK Complete.[28] Nucleic acid tests are highly sensitive and specific for diagnosis of CDI.[29] There are many FDA approved NAATs available one of which is Xpert C. difficile Assay which has a sensitivity and specificity of 100% and 93% respectively.[30] Use of toxin assay as the sole test will lead to missing diagnosis of CDI in 5% to 25% of cases. Even in our study in which clinicians were looking for CDI, NAAT was not ordered in 48% of the patients, possibly due to higher cost.

CDI is found to be more common in older age group with varying male to female ratio in India.[20,31] In our study the mean age was 52.16 ±14.13 years and males were in slightly higher proportion (60%). CDI can range from mild to severe disease. Mild disease is characterized by diarrhea without colitis. Patient with moderate disease

will have diarrhea with features of colitis like abdominal cramps and fever. Severe disease is characterized by diarrhea, leucocytosis (>15000 cells/μL), hypo-albuminemia (<3gm/dL) and high creatinine (> 1.5 times then premorbid levels).[32] In our study we found four patients with mild, 10 with moderate and 4 with severe disease. In comparison analysis we found that presence of fever, cramps, tenesmus and hematochezia was found to be significantly associated with CDI as compared to controls. However, frequency and duration of diarrhea were not significantly different. Ingle et al also found that presence of fever was significantly associated with CDI. There was a trend towards more presence of clinical symptoms like cramps, hematochezia and tenesmus in CDI group however it was not statistically significant.[19] Pseudomembranous colitis can be caused by a number of disease states, and was noted in 3 patients. It is a non-specific pattern of injury which results from decreased oxygenation, endothelial damage, and impaired blood flow.[33]

Antibiotic usage is a common cause of diarrhea and is implicated in CDI. Among antibiotics exposure to clindamycin, cephalosporins and fluoroquinolone is maximally associated with CDI.[34,35] Other risk factors for CDI include malignancy, use of immunosuppressants, ICU stay, exposure to PPI and smoking.[36,37] In Indian studies exposure to PPI, use of immunosuppressive agents, ICU stay and malignancy have been found to be significant risk factors for CDI.[19] These findings were also reciprocated in our study.

Metronidazole and vancomycin are the major agents which are used in treatment of CDI. For mild to moderate disease 10 days of oral metronidazole is recommended whereas oral or per rectal vancomycin for 10 days is used for severe disease.[32] In our study 10 patients were treated with metronidazole (they were having mild to moderate disease); eight were given vancomycin severe disease) those with as the first drug. The median duration of treatment was 8.55±1.72 days.

Our study has certain limitations. Firstly it being a retrospective study only those samples were analyzed in whom the treating physician suspected CDI giving this study a selection bias. Secondly most of our study stool samples were tested for toxin assay only leading to an underestimation of prevalence of CDI among nosocomial diarrhea. Thirdly we did not include a control group of patients without diarrhea.

In conclusion, CDI is an underestimated disease in India and accounts for at least 16% of hospital acquired diarrhea. Clinical clues to the diagnosis include fever, cramps, tenesmus and hematochezia. Prevalence may be even higher if more sensitive tests such as NAAT are used. Our study emphasis on the already established risk factors (antibiotic exposure, immunosuppressive therapy and PPI). We recommend prompt testing with NAAT in any patient with hospital acquired diarrhea, especially in the presence of the risk factors and symptoms above.

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