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Antibiotic-Associated *Clostridium difficile* Diarrhoea in Tertiary Care Hospital – A Study from Western India

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Abstract

Antibiotic-associated *Clostridium difficile* (CD) diarrhoea is one of the common causes of healthcare-acquired infection. Cephalosporins, piperacillin-tazobactam and aminoglycosides are the common antibiotics which have the maximum chances of producing *Clostridium difficile* infection (CDI). Most Asian countries have easy accessibility to many of these antibiotics without prescription. Broad spectrum antibiotics have been indiscriminately used as empirical therapy over the last two decades which has resulted in an increased risk of *C. difficile* infection. In India, the prevalence of CDI is highly underestimated. This study aims to understand the prevalence, risk factors and comorbidities associated with CD diarrhoea in a tertiary care hospital from western India. 196 patients were included in the study who were diagnosed with antibiotic-associated diarrhoea (AAD) clinically. Stool samples collected were processed for anaerobic culture of *C. difficile* and immunochromatography test was done to detect *C. difficile* toxins A and B. The comorbidities associated as well as the use of antibiotics like cephalosporin or proton pump inhibitors were also noted for the patients with CDI. 32 samples yielded CD (16%), out of which toxin production was detected only in 16 isolates. The prevalence rate of CDI in our hospital was 5%. Most of the patients had history of chronic illnesses like diabetes mellitus, chronic kidney disease, ischemic heart disease, systemic hypertension, autoimmune diseases, or malignancy. Avoiding empirical therapy with antibiotics prone to cause AAD, Antimicrobial stewardship programme with proper infection control practices and epidemiological surveillance of CDI will help to reduce the burden of CDI in our country.

Keywords: Antibiotic-Associated Diarrhoea, *Clostridium difficile* Infection, Comorbidities, Risk Factors, Toxins

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INTRODUCTION

CD is an important causative agent of antibiotic-associated diarrhea (AAD) resulting in significant mortality and morbidity all throughout the world.[1,2]

Clindamycin, cephalosporin, fluoroquinolones and carbapenems have the maximum risk of developing CDI.[3] Antibiotics alter the normal microbiota, increasing the risk of infection with *Clostridium difficile*. Toxin A &B production is the key to the pathogenesis resulting in watery diarrhoea, abdominal pain, fever and nausea.[4-6] Risk factors associated with CDI include old age, chronic kidney disease, recent hospitalization, use of proton pump inhibitors, chemotherapy and tube feeding.[1,7,8]

Asymptomatic colonization and clinical infection cannot be differentiated by laboratory testing alone. Presence of diarrhoea along with stool positivity for *C. difficile* toxins, or histopathology/ colonoscopy findings suggestive of pseudomembranous colitis is required for the diagnosis of CDI.[7,9,10] Vancomycin, metronidazole and fidaxomicin are the drugs recommended for the treatment of CDI.[11]

In developing countries, there is a lacuna in data on CDI. This could be due to the lack of awareness about the infection, poor capacity of the laboratory and insufficient mechanisms for surveillance.[3,12] This study was done in a tertiary care hospital from western India to observe the prevalence, risk factors and comorbidities associated with CD diarrhoea.

MATERIALS AND METHODS

The present study is an observational, cross-sectional study done in the Department of Microbiology from August 2018 to June 2022. 196 patients were included in the study who were clinically suspected of having antibiotic-associated diarrhoea (AAD). Patients were clinically suspected as having AAD if they presented with watery

Table. Patients who were positive for Glutamate dehydrogenase(GDH) and Toxins of CD

No.	age	sex	Location	Diagnosis	Prior antibiotics, PPI,
1.	45	F	Medicine	Right lower limb deep venous thrombosis, Chronic Kidney Disease on haemodialysis	Amoxicillin -clavulanate
2.	36	F	Medicine	Myasthenia gravis, SLE	Cephalosporins & Colistin
3.	63	M	ICU	Road traffic accident, Diabetes mellitus (DM)	Cephalosporins
4.	24	M	Surgery	Intestinal obstruction Post-operative	Cephalosporins
5.	38	M	Medicine	Enteric fever	Cephalosporins
6.	70	M	ICU	DM, Heart disease, Ischemic colitis	Piperacillintazobactam, PPI
7 .	38	M	Surgery	Fall from height Head injury	Meropenem, PPI
8.	57	M	ICU	DM, Hypertension (HTN), Tracheostomy	Cephalosporins PPI
9.	74	F	Surgery	Endometrial sarcoma	Cephalosporin, PPI
10.	56	M	ICU	DM, HTN, COVID	Meropenem,PPI
11.	30	F	Medicine	COVID pneumonia	Meropenem
12.	50	M	Medicine	Tracheoesophageal fistula, AIDS on ART, on prophylactic ATT	Ciprofloxacin,Pipera cillin-tazobactam,colistin, meropenem, PPI
13.	37	M	Medicine	Ulcerative colitis, IBD	Vancomycin, Meropenem, PPI
14.	78	M	ICU	DM, CKD	Meropenem,PPI
15.	51	M	Medicine	Acute Myeloid Leukemia(AML)	Ciprofloxacin, Meropenem, Colistin, Teicoplanin, Doxycycline, PPI
16.	44	F	ICU	AML	Cefoperazonesulbactam. Vancomycin, Fluconazole

Abbreviations used- Sex: M-male, F-female, SLE- Systemic lupus erythematosus, RTA-Road traffic accident, PUO- Pyrexia of unknown origin, AIDS- Acute immunodeficiency syndrome, ART-Antiretroviral therapy, ATT- Anti tuberculosis therapy, IBD-Inflammatory bowel disorder, CKD-Chronic kidney disease

diarrhoea along with a history of usage of antimicrobial agents over the previous two weeks. Patients who had diarrhoea caused by other microbes or other factors inducing diarrhoea were excluded from the study. Collection of stool samples were done in wide mouth, screw capped, sterile containers and further processing was done in the microbiology laboratory. Standard anaerobic methods were used for stool culture of *C. difficile* after which rapid immunochromatography test was done for detection of *C. difficile* toxins A and B. If AAD was present along with the presence of *C. difficile* toxin, the patient was confirmed to have CDI.

RESULTS

196 stool samples were processed from patients with suspected AAD. 32 samples yielded CD (16%), out of which only 16 isolates produced toxins (5%) (Figure 1), (Table). Out of the 32 CDI positive patients, 20(62.5%) were males and 12(37.5%) were females. 71.8% of the patients with CDI were above 40 years of age (Figure 2). 15 patients were admitted in the ICU's while 13 patients were in medicine ward and four in surgery ward. All patients were on antibiotics and 18 were on proton pump inhibitors (PPI). Most of the patients had history of chronic illnesses like chronic kidney disease, diabetes mellitus, ischemic heart disease, systemic hypertension, malignancy or autoimmune diseases (Figure 3).

DISCUSSION

In spite of being a major agent responsible for AAD in the Europe and US, CD is majorly

Figure 1. CD toxin detection by rapid immunochromatography

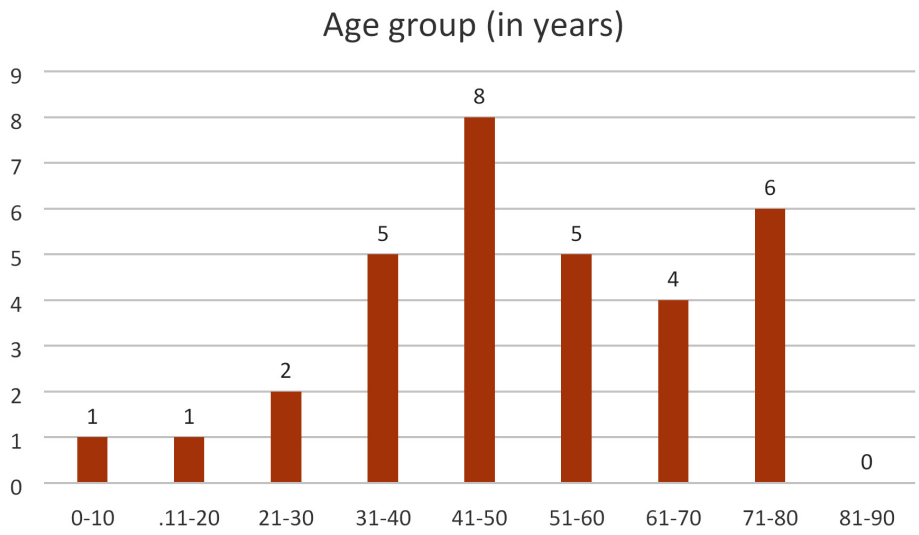

Figure 2. Age distribution of the patients

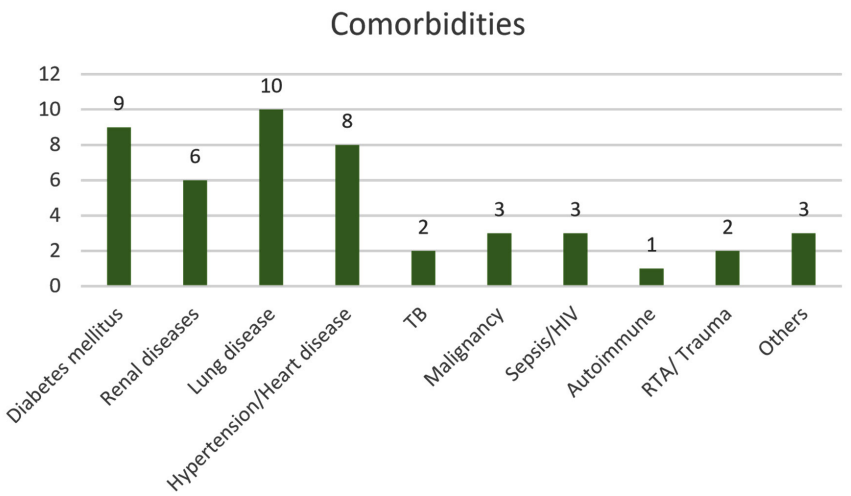

Figure 3. Comorbidities among patients

neglected in India.[3,13] In developing countries like India; the prevalence of CDI is majorly underestimated. In a study done by Ghi et al., a prevalence rate of 3.4% to 18% was found for CDI in India.[3] The prevalence rate in our study was found to be 5%. This was similar to the study done by Segar et al. where the prevalence of CDI was 4%.[14] But many studies in India have shown higher prevalence rate of CDI, like the 17% in a study done by Ingle et al., from western India (2011), 18% by Kannambath et al., from southern India (2021), 11% by Vaishnavi et al., from northern India (2015) and 9.6% by Niyogi et al., from eastern India (1991).[3,15,16] The reason for the lower prevalence could be due to the adhesion to the antibiotic policy adopted in our hospital and strict implementation of infection control practices.

CDI is commonly associated with older age group (> 65 years) predominantly due to the increased exposure to medications, presence of many comorbidities and more frequent hospitalization.[15,17] Our study had majority of the isolates of *C. difficile* from patients in the 41-50 years' age group. Many Indian literatures have shown a male predominance in the development of CDI.[3,18,19] The CD infected patients in our study were 62% males and 37% females. The data from Centres for Disease Control and Prevention's Emerging Infections Program surveillance done in 2011 has shown a higher incidence of CDI in females.[20]

The patients who developed CDI in the present study were admitted for various clinical disorders. Majority of the patients had diabetes mellitus/ systemic hypertension or both. Studies have demonstrated that diabetes increases the risk of recurrent CDI.[21] Other comorbidities associated with our patients were ischemic heart disease, chronic kidney disease, malignancy and autoimmune diseases. Damage to the gastrointestinal epithelium caused by the CD toxins cannot be delayed or prevented in immunocompromised patients.[1]

All patients in our study were on antibiotics or PPI. In the literature review done by Ghia et al., [22] articles showed that all the people developed CDI who were on prior antibiotics.[3] Disruption of the normal gastrointestinal flora occurs as a result of prolonged antibiotic use resulting in decreased defences of body against *C. difficile*, which can easily produce toxins.[22] Piperacillin-tazobactam is associated with 1.5 time's higher risk of developing CDI as per National Institute of Health and Care Excellence (NICE). Among the antibiotics that have increased risk of causing CDI, cephalosporins rank among the highest.[1,23] Antibiotics commonly used in our patients in the study were third generation cephalosporins, piperacillin-tazobactam or meropenem. Colonization and infection with CD can also be stimulated by acid suppression due to usage of PPI.[16] In our study,18 out of 32 patients were on PPI. This could also have promoted the development of CDI in these patients.

In our study in 16% the samples, GDH was positive without toxin production. In a study done by Akamatsu et al.[24], out of the 356 GDH positive/ toxin negative patients, cultures were done in 220 samples and toxin producing *C. difficile* was obtained from 139 (63.2%) samples.[24] Therefore such population who are GDH positive/toxin negative, should be monitored carefully. Also, the effect of *C. difficile* colonization varies in different patients (asymptomatic carrier state to fulminant colitis and death). The extend of interaction between the virulence factors produced by the bacterium and the immune responses against it by the host play a major role in determining this effect.[25] Most of the patients in our study who were GDH positive and toxin negative were having comorbidities like diabetes mellitus, systemic hypertension, heart disease, lung disease or autoimmune disease.

In countries with limited resources like India, besides the costly anaerobic culture techniques, lack of routine testing in patients with diarrhoea, usage of suboptimal testing methods creates more challenges the detection of CDI.[3]

CONCLUSION

Significant presence of CDI in this hospital population is demonstrated by this study. Cephalosporins, piperacillin-tazobactam and carbapenems were found to be the most common agents responsible for AAD caused by CD. Occurence of CDI may be reduced by choosing the antibiotic which has lower risk of producing AAD, from the susceptibility panel as well as avoiding the usage of β-lactam and β-lactamase inhibitors (BL-BLIs) as empirical therapy. The development of multidrug-resistant (MDR) strains of CD can be reduced by implementing proper infection control practices. In developing countries like India, knowledge of epidemiological patterns of CDI will help to develop useful strategies for the prevention and control of CDI.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

This study was approved by Bharati Vidyapeeth Medical College, Institutional Ethics Committee, Pune, India, with reference numbers BVDU/MC/E20 and BVDUMC/IEC/92.

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