ORIGINAL RESEARCH PAPER

Volume - 10 | Issue - 06 | June - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

PREVALENCE OF CLOSTRIDIUM DIFFICILE INFECTION IN PATIENTS EXPOSED TO ANTIBIOTICS IN PREVIOUS 6 WEEKS AND ADMITTED WITH DIARRHEA IN A TERTIARY CARE HOSPITAL.

Gastroenterology

Dr Sanjay Kumar Singh*	Senior Resident,Gastroenterology, Max Hospital , Saket,N Delhi.*Corresponding Author
Dr. Ashwini Kumar Setya	Senior Consultant, Gastroenterology, Max Superspeciality Hospital, Saket, New Delhi.
Dr Abhishek Deo	Consultant,Gastroenterology, Max Hospital, Saket, New Delhi.
Dr Vivek Raj	Senior consultant, Gastroenterology,Max Hospital, Saket, N Delhi.
Dr Suneel Chakravarty	consultant, Gastroenterology, Max Hospital saket, N Delhi.

KEYWORDS

INTRODUCTION:-

Clostridium difficile is a significant cause of morbidity and mortality among hospitalized patients, and the incidence of *C. difficile* infection (CDI) has dramatically increased due to frequent usage of broad-spectrum antibiotics in these patients. The wide variation in the spectrum of clinical manifestations of CDI makes the diagnosis difficult. Further, the wide range of variability in the sensitivity and specificity of the various diagnostic methods and the high cost of these methods add to the difficulty. It is a spore-forming gram-positive anaerobic organism. Until the 1970s, it was considered as a microorganism that is rarely present in normal intestinal microbiota. But it was not until 1978 that C. difficile was identified as a cause of pseudomembranous colitis [1]. Since then, C. difficile has been recognized as a common cause of antibiotic associated diarrhoea and nosocomial diarrhoea. The incidence of C. difficile infection (CDI) varies from place to place. In India, it is known to infect up to 25 % of people taking antibiotics [2].

MATERIALS AND METHODS:-

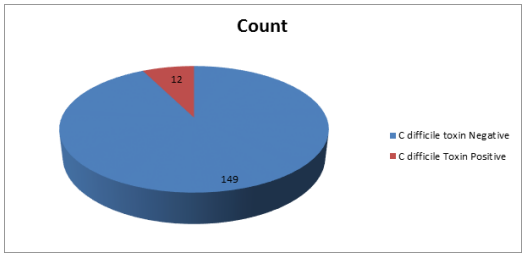
The is a prospective prevalence study, conducted in Department of Gastroenterology, and Microbiology, Max SuperSpeciality Hospital, Saket, New Delhi. In this study, clostridium difficile toxin assay was done from stool samples of patients admitted with diarrhoea in a the hospital and had history of antibiotic use in last 6 weeks. All hospitalized patients age > 18 years, with acute diarrhea (for more than 24 hrs, with or without blood in stool, increased frequency ≥3 times /day, and consistency -Bristol stool chart types 4-7) [3] and had a recent history of exposure to antibiotics previous 6 weeks. Patients with age < 18 years, with formed stools (Bristol stool types 1, 2, 3), those who have been treated for documented Clostridium difficile infection and patient with acute diarrhoea due to other cause (viral, protozoa, or parasitic) after doing relevant stool tests including Multiplex PCR were excluded from the study.

The stool was tested for C difficile toxin by doing Enzyme immunochromatography assay. Stool for Clostridium difficile toxin PCR (polymerase chain reaction) was done for patient with recurrent diarrhoea and negative assay for stool clostridium difficile toxin and high clinical suspicion of CDI. Sigmoidoscopy was performed in patients with negative assay of clostridium difficile toxin assay, but having persistent diarrhoea for >72 hours after first evaluation and high clinical suspicion, and to look for alternative pathology for diarrhoea (e.g Inflammatory bowel disease, Microscopic colitis).

RESULTS:-

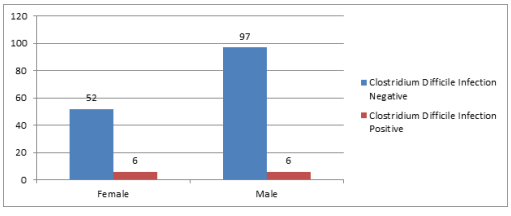
In our study, prevalence of clostridium difficile infection was studied in the hospitalized patients with diarrhea, who had been exposed to antibiotics in previous 6 weeks prior to the hospitalization. The data was collected prospectively. Stool was tested for clostridium difficile by enzyme immunochromatographic assay and PCR assay. Either of these tests showing positive results was interpreted as clostridium difficile infection. In total of 161 patients tested, 12 patients tested positive for CDI, which was 7.5 % of the population studied. While 92.5 % patient tested negative for CDI as shown in pie chart below. Of the 12 tested positive for CDI, 9 patients were PCR positive, while rest 3 tested positive by enzyme immunochromatography assay

Pie Chart showing prevalence of CDI in studied population.



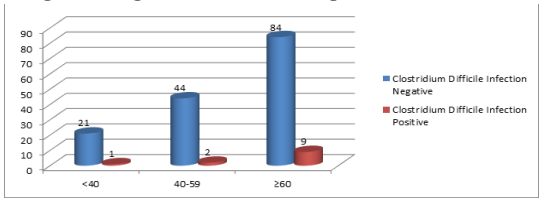
Gender-wise analysis was done for all patients and it was found that, out of all patients, 103 patients were males (64%) and 58 patients were females (36%). While among the patients with positive assay for clostridium difficile, it was found that 6 males and 6 females were affected. While in patients with negative assay for clostridium difficile infection, 52 patients were females and 97 patients were male as shown in bar diagram 1.

Bar diagram 1 :- Gender wise distribution of Prevalence of CDI



Age wise prevalence of CDI was studied, and as per the inclusion criteria patients >18 yrs of age with diarrhea in hospital were included. As shown in bar diagram 2 below, in age group <40 yrs (i.e. 18-40 yrs), 21 patients were found to be negative for CDI, while only 1 patients was found with positive assay for C difficile toxin. In age group 40-59 yrs, there were 44 patients who tested negative for CDI, while 2 patients tested positive for C difficile assay. The maximum number of patients was found in ≥ 60 yrs age group. In this subgroup 84 patients tested negative for C difficile, while 9 patients tested positive for CDI. Hence overall prevalence of CDI was higher in patients in older age group.

Bar diagram 2 : Age wise distribution of prevalence of CDI



Association of common antibiotics associated with clostridium difficile infection:

Subsequently we studied the common antibiotics associated with CDI. Among all these antibiotics, Carbapenam (in form of meropenem, dorepenem), was used in maximum number of patients who developed diarrhoea. In patients with negative assay for CDI, 60 patients out of 149 had been exposed to meropenem, while only 5 out of 12 patients who had tested positive for C difficile, had previous exposure to carbapenem. Among patients who tested negative for CDI, 48 patients had exposure to cephalosporins (in form of ceftriaxone, ceforperazone and sulbactum, ceftazidime) while 3 patients with positive assay of CDI had been exposed to cephalospsorins as shown in table 1.

Although some patients were also exposed to other group of antibiotics, but their number was low and they were not analyzed for interpretation of data. As per the data the association of,various antibiotics was studied with development of diarrhea, and the individual drugs was analyzed separately for association using Fisher T test, and P value was calculated

Table no.1 Antibiotics associated with CDI & AAD:

Antibiotics Associated		Clostridium Difficile Infection				Total
		Negative		Positive		
		Count	%	Count	%	
Carbapenam	Yes	60	92.3%	5	7.7%	65
Cephalosporin	Yes	48	94.1%	3	5.9%	51
Colistin	Yes	18	94.7%	1	5.3%	19

It was found that in patients exposed to carbepenem and colistin group of antibiotics the P value was 1. While in cephalosporins group the P value was 0.75. hence it was found that there was no difference in prevalence of diarrhoea (either C difficile positive or negative) amongst the 3 group of antibiotics.

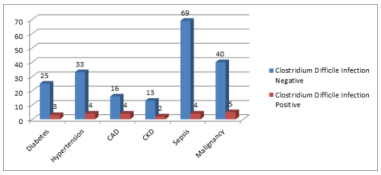
Common disorder associated with clostridium difficile infection:

We further studied the association of common underlying medical conditions with C difficile diarrhoea prevalence. Broadly we studied common disease including diabetes, hypertension, chronic kidney disease (CKD), Coronary artery disease (CAD), and sepsis. As shown in bar diagram 3, it was found that out of all underlying conditions, patients with sepsis had maximum incidence of diarrhea. Sixty-nine (94.5%) patients out of 73 diagnosed with sepsis tested negative for CDI, while 4 patients (5.5%) tested positive for CDI. Second most common variable was malignancy which was found in 45 patients (27.75%) with diarrhoea out of 161. Out of 149 Patients negative for CDI, 40 patients (26.84%) were found to have underlying malignancy.while out of 12 patients with CDI, 5 patients were found to have underlying malignancy. This was also studied with respect to the positivity of CDI, and it was found that malignancy was not significantly associated with AAD or CDI.

In 28 patients of the diabetic group, altogether 25 patients (89.3%) had diarrhea with negative assay for CDI, and 3 patients (10.7%) had positive assay C difficile toxin. While in patients with hypertension, out of 37 patients, 33 patients (89.2%) were negative for CDI, whereas, 4 patients (10.2%) tested positive for CDI. However the number of patients with CKD and CAD developing diarrhea were lower. It was found that 16 patient with negative assay for CDI, had underlying CKD, while 13 patients had underlying CAD. While in patients with positive CDI, 4 patients had CKD, and 2 patients had underlying CAD.

Furthermore the association of various disorders with development of CDI was analyzed and the data was interpreted using Chi Square Test. The P value was calculated as per this, and it was found that the patients with diabetes had P vales of 0.44; hypertensive patients had P value of 0.47. Hence these two disorders were not significantly associated with C. difficile infection. Similarly patients with CAD and sepsis were studied, and their data was analyzed using Chi Square test and P value was found to be 0.31 and 0.38 for patients with CAD and sepsis respectively.

Bar diagram 3 : Association of comorbidity with CDI



Specificity of the polymerase chain reaction (PCR) was calculated as True Negative/True Negative + False positive. It was found that specificity of PCR was 100%. Negative Predictive Value (NPV) was calculated as True Negative/True Negative + False Negative. It was found to be 94.3 % as shown in table 2 below.

Table 2: Test results of EIA and PCR in study population

ELISA	PCR Test		
	Positive	Negative	Total
Positive	0	0	0
Negative	9	149	158
Total	9	149	158

Specificity = 149/149 = 100%
NPV = 149/158 = 94.3%

The study design precluded the calculation of sensitivity and positive predictive value of Enzyme immunochromatography assay.

Sigmoidoscopic examination was done in patients with negative assay for CDI, with high clinical suspicion of CDI and in those with persistent diarrhoea to exclude other etiologies like inflammatory bowel disease, microscopic colitis, malignancy and infective colitis due to other cause. Few patients underwent this procedure as most of the patients improved.

Sigmoidoscopic was done in 8 patients altogether, in which 7 patients had been tested negative for CDI, while 1 patient had tested positive for CDI. Infective colitis was seen in 2patients on basis of histopathological examination, while adherent clot in caecum, colonic polyp, and hemorrhoids were seen in 1 case each.Two patient had normal sigmoidoscopy.One patient with positive assay for CDI, underwent sigmoidoscopy which was suggestive of ulcer, and pseudomembrane overlying it. One hundred fifty three out of 161 did not undergo sigmoidoscopy patients, including 142 patients who tested negative for CDI, and 11 patients with positive assay for CDI as shown in table 3.

Table 3. Sigmoidoscopic finding in the studied subjects

Sigmoidoscopy	Clostridium Difficile Infection			
	Negative		Positive	
	Count	%	Count	%
Altered Adherent Clot In Terminal Ileum, and Caecum, Rest Normal Sigmoidoscopy	1	0.7%	0	0.0%
Colonic Polyps (Not biopsied-patient on antiplatelets)	1	0.7%	0	0.0%
Diffuse ulceration with pseudomembrane over them, rectal biopsy luminal pseudomembrane like structure, but activity or typical crypt changes not seen, suggestive but not definitive of pseudomembranous colitis	1	0.0%	1	8.3%
Hemorrhoids Seen, rest Normal Study	1	0.7%	0	0.0%
Normal Sigmoidoscopy	1	0.7%	0	0.0%
Petechial Spots In Caecum- Biopsy-Patchy Mild Edema, Mild Increased Lymphocytic Infilteration.	1	0.7%	0	0.0%
Rectocele,redundent sigmoid colon with poor tone	1	0.7%	0	0.0%
Right sided colitis. Internal hemorrhoids . Biopsy s/o focal acute/active colitis, mild cryptitis, spotty low grade dysplasia s/o infective etiology (?resolving phase)	1	0.7%	0	0.0%
Not Done	142	95.3 %	11	91.7%

In Summary of results, the prevalence of CDI in our study population was found to be 7.5 %. It was found equally prevalent in males and females. It was more common in higher age group ≥ 60 yr, while that was not statistical significant. However, the prevalence was commonly seen with antibiotics Carbapenem,, but that too was not found to be statistically significant. Only patient with underlying CKD, were found to be significantly associated with CDI, Rest other comorbidities

like Diabetes, hypertension, CAD, Sepsis, were not associated with higher prevalence of CDI. Routine stool examination was found to be normal in majority of cases be it either CDI or AAD. Stool C difficile, PCR was found to be 100 % specific, and had 94.3 % Negative predictive value. Sensitivity of both tests, and Positive predictive value of Enzyme immunoassay could not be tested due to the available results and study design. Sigmoidoscopic examination was done in limited number of cases as most of the patients improved, and some of them died in AAD group (negative assay for CDI).

DISCUSSION:-

In our prospective observational study from 2019 to 2020, we have studied the prevalence of Clostridium difficile infection (CDI), in patients exposed to antibiotics in previous 6 weeks, and admitted with diarrhea in a tertiary care hospital. The prevalence in our study was found to be 7.5 %. This was above the prevalence found in study by Segar et al [7] and Singhal et al [9], in which it was found to be 4% and 4.9% respectively. Our study prevalence value was lower than the value found in the studies done by Igle M et al[4], Chaudhary et al[5], Singh M et al[6], Vishwanath et al [8], and Chakravarty et al [10].

Our study design was prospective and observational, while Segar et al [19] was a prospective cohort study, at JIPMER Puduccherry, and Singhal et al [21] was retrospective study at Kokilaben hospital Mumbai. Among other studies which showed higher prevalence, study by Igle M et al [4] was a retrospective study done at Mumbai and that by Chaudhary R et al [5] was a cross sectional study done at AIIMS done in 2014. Another study by Singh M et al [6] was an observational study done at PGIMER, Chandigarh. Vishwanath S and coworkers [8] did a prospective pilot study at Manipal, Karnataka and study by Chakravarty et al [10] was a retrospective observational study done at Kolkata.

In our study, out of all underlying comorbidity, CKD was found to be significantly associated with the development of CDI (P-value- 0.045). All other conditions viz Sepsis, Diabetes, hypertension, CAD, were not found to be statistically significantly associated with CDI.

In a study done by Kim S C et al[11], at Seoul, Korea, which was a single-centre retrospective case control study 71 patients with CDI were included as disease subjects and 342 age and gender matched without CDI, were used as the control subjects. The Prevalence of CKD was compared in both groups. It was found that CKD was an independent risk factor for CDI. Moreover patients with more advanced CKD (estimated glomerular filtration rate eGFR <30), and CDI showed high in hospital mortality.

A similar study done by Keddis T M et al [12], at mayo clinic, they examined the rate of CDI and hospital associated outcome in a national cohort of hospitalized patients. CDI rate in CKD was compared with Patients without CKD. CKD patients not on dialysis had a higher incidence of CDI than non- CKD patients ($p < 0.001$). It was found that patients with CKD and CDI had longer hospitalization and increased in hospital mortality. Our data is in keeping with these two studies.

REFERENCES

1. Barlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Eng J Med 1978; 298: 531-4.
2. Dhawan B, Chaudhry R, Sharma N. Incidence of Clostridium difficile infection: a prospective study in an Indian hospital. J Hosp Infect. 1999;43:275–80
3. Bristol stool chart. https://www.continence.org.au/pages/bristol-stool-chart.html.
4. Ingle M, Deshmukh A, Desai D, Abraham P, Joshi et al. Prevalence and clinical course of Clostridium difficile infection in a tertiary-care hospital: a retrospective analysis.Indian J Gastroenterol 2011;30(2):89–93.
5. Chaudhry R, Sharm N, Gupta, N, Kant K, Bahadur T. Nagging Presence of Clostridium difficile Associated Diarrhoea in North India. JCDR 2017;11(9):DC06-DC09.
6. Singh M, Vaishnavi C, Rakesh Kochhar R, Mahmood S. Toxigenic Clostridium difficile isolates from clinically significant diarrhea in patients from a tertiary care center; Indian J Med Res 145, June 2017, pp 840-846DOI: 10.4103/ijmr.IJMR_192_16.
7. Segar L, Easow M, Srirangaraj S, Hanifah M, Joseph N, Prevalence of Clostridium difficile infection among the patients attending a tertiary care teaching hospital; Indian J Pathol Microbiol 2017;60:221-5.
8. Vishwanath S, Singhal A, D'Souza A, Mukhopadhyay C, Varma M, Bairy I. Clostridium difficile infection at a tertiary care hospital in south India.J Assoc Physicians India. 2013 Nov;61(11):804-6.
9. Singhal T et al, Shah S, Tejam R, Thakkar P et al. Incidence, epidemiology and control of *Clostridium difficile* infection in a tertiary care private hospital in India. Indian journal of medical microbiology; 2018: 36. 3;381-384.
10. Chakraborty A, Kar A, Roy S. Changing trends of *Clostridium difficile* associated diarrhea (CDAD) in a tertiary care hospital in Kolkata, India. Intensive Care Med Exp 2015;3:A118.
11. Sun Chul Kim, Min Young Seo; Advanced chronic kidney disease: a strong risk factor for *Clostridium difficile* infection.Korean J Intern Med 2016;31:125-133.
12. Keddis T M, Khanna H, *Clostridium difficile* Infection in Patients with Chronic Kidney Disease. 2012 Mayo Foundation for Medical Education and Research Mayo Clin Proc. 2012;87(11):1046-1053.