Original Article

Clostridium difficile infection: Is there a change in the underlying factors? Inflammatory bowel disease and *Clostridium difficile*

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Abstract

Background / Aims: *Clostridium difficile* is a Gram-positive, strict anaerobe, spore-forming bacterium. It can cause self-limiting mild diarrhea, severe diarrhea, pseudomembranous colitis, and fatal fulminant colitis. We aimed to investigate the changes in epidemiology and incidence of *C. difficile* infection in our hospital database.

Patients and Methods: Episodes of *C. difficile* toxin were identified in hospital database, and data such as age, sex, community versus hospital acquisition, intensive care follow-up, current or previous treatments with antibiotics within the past 3 months, medication with proton pump inhibitors, or immunosuppressive therapies were collected.

Results: Toxin-positive 78 individuals constituted the patient group. In univariate analyses, independent risk factors for toxin positivity were community versus hospital acquisition [odds ratio (OR), 5.49; 95% confidence interval (CI), 2.52–11.95; $P = 0.0001$], presence of inflammatory bowel diseases (IBDs) (OR, 21.5; 95% CI, 8.65–53.44; $P = 0.0001$), proton pump inhibitors' use (OR, 4.53; 95% CI, 1.97–10.43; $P = 0.0001$), immunosuppressive drug use (OR, 4.1; 95% CI, 2.01–8.3; $P = 0.0001$), and use of quinolone group of antibiotics (OR, 5.95; 95% CI, 1.92–18.46; $P = 0.001$). Antibiotic use was a protective risk factor (OR, 0.09; 95% CI, 0.01–0.78; $P = 0.01$) and presence of IBDs was an independent risk factor (OR, 6.8; 95% CI, 1.5–30.08; $P = 0.01$) in community-acquired group (OR, 0.09; 95% CI, 0.01–0.78; $P = 0.01$).

Conclusion: In recent studies, *C. difficile* infections were demonstrated to be more frequent in younger individuals who did not have a history of hospitalization but had an underlying disease such as IBD. In our study, we showed the change in the epidemiological data with prominence of underlying diseases such as IBDs.

Keywords: Antibiotics, *Clostridium difficile*, inflammatory bowel disease, risk factors, Turkey

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INTRODUCTION

Clostridium difficile is a Gram-positive, strict anaerobe, spore-forming bacterium.[1] It can cause self-limiting mild diarrhea, severe diarrhea, pseudomembranous colitis, and fatal fulminant colitis.[2] The bacterium was first detected in the meconium of a newborn in 1935,[3] and until the

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end of 1970s it was considered as a commensal organism. In 1978, it was first realized that the bacterium was the causative agent for pseudomembranous colitis and from thereon to the 21st century, the incidence has increased.[4,5]

Nosocomial *Clostridium difficile* infection (CDI) occurs generally in older patients with chronic diseases and a history of antibiotic use in contrast to community-acquired CDI which occurs generally in younger patients, in whom estimated risk factors such as chronic diseases, antibiotic use and hospital stay are absent.[2,6] Several studies reported that community-acquired CDI was associated with underlying intestinal diseases rather than well-known risk factors. Community-acquired CDI incidence is increasing comparable to that of inflammatory bowel disease (IBD) especially in East European countries.[7,8] We aimed to investigate the changes in the epidemiology and the incidence of CDI in our hospital database.

PATIENTS AND METHODS

Study design and patients

This retrospective case–control study was conducted in our 586-bed hospital. Approximately, over 1 million outpatients and 100,000 inpatients are treated in this hospital per year. Episodes of *Clostridium difficile* toxin (CdTx) were identified retrospectively from September 1, 2014, to October 1, 2016. Patients were included if they were 18 years of age or older on admission, had acute hospital-acquired diarrhea or a diarrhea which started before hospitalization, and were an outpatient with diarrhea. Exclusion criteria were a history of chronic diarrhea, human immunodeficiency virus infection, and a diarrhea which is not amenable to treatment or which is a reactivation in patients with IBD. Toxin-positive individuals constituted the patient group. A corresponding control group was constituted by selecting a random patient among every eight patients after all admissions were arranged by date in consecutive order. Hospital database was searched for data of all patients. CdTx-positive individuals were grouped into colonization and infection subgroups according to CDI diagnosis criteria. CDI was defined as the presence of diarrhea (>3 loose stools/day)[1] and a positive CdTx A or B test. Two episodes in the same patient were considered as different events if they occurred >8 weeks apart (after the toxin became negative). Collected data included age, sex, community versus hospital acquisition, duration of hospital stay, intensive care unit (ICU) follow-up history, duration of ICU stay, comorbidity, current or previous treatments with antibiotics within the past 3 months, medication with proton pump inhibitors (PPIs),[9] or immunosuppressive therapies. Antibacterials were grouped into four classes: β-lactam/β-lactamase inhibitor combinations, carbapenems, cephalosporins, and fluoroquinolones. Treatment regimens and results as well as mortality were not assessed in this study.

Community-acquired and hospital-acquired CDI definitions[10]

Community-acquired CDI

Onset of symptoms occurs in the community or within 48 h of admission to a hospital (after no hospitalization in the past 12 weeks).

Hospital-acquired CDI

Onset of symptoms occurs more than 48 h after admission to or less than 4 weeks after discharge from a healthcare facility.

Detection of CdTx

We used commercially available test CerTest *C. difficile* glutamate dehydrogenase (GDH) + toxin A + B one-step combo card test (Biotec, Spain) to detect CdTx. This is a colored chromatographic immunoassay for the simultaneous qualitative detection of *C. difficile* GDH, toxin A, and toxin B in stool samples. The test offers a simple and highly sensitive screening assay to make a presumptive diagnosis of *C. difficile* infection. The results were interpreted according to the manufacturer's guide.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS), version 17 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analyses. Categorical variables were presented as the number of cases and percentages. Continuous variables with a normal distribution were presented as mean ± standard deviation, and continuous variables without a normal distribution were presented as median [interquartile range (IQR)]. Categorical variables were compared using a Chi-square test. Continuous variables with and without a normal distribution were compared using a two-tailed Student's *t*-test and a Mann–Whitney *U*-test, respectively. Binary logistic regression ("backwards: LR" method) was used for multivariate analysis. A *P* value of ≤0.05 was considered statistically significant.

Ethical considerations

Local ethics committee of the hospital approved the study.

RESULTS

A total of 1486 stool samples of 1251 patients were collected during the study period. Of those, 787 samples of 549 patients were excluded due to a lack of concordance with the study protocol and 702 patients were included

in the study. Among included patients, CdTx-positive 78 individuals constituted the patient group. The control group was constituted among toxin-negative 624 individuals by a 1:1 ratio. Of toxin-positive patients, 13 (16.7%) were colonized and 65 (83.3%) were infected with *C. difficile*. The mean age of patient group was 41.3 ± 16.3 years, and 41 (52.6%) were female. CdTx became positive in median 10th (IQR, 5.5–30) day of hospital stay in inpatients. Although there was no mortality in case group, five individuals died in the control group.

Of the included patients, 48 were hospitalized. A history of ICU stay was present in eight of the hospitalized patients. The median length of hospital stay was 19 (IQR, 13–24) days. The length of hospital stay was longer in CdTx-positive patients, but the difference was not statistically significant (P = 0.245). The median age of CdTx-positive patients was higher than that of toxin-negative patients (P = 0.001).

In univariate analyses [Table 1], independent risk factors for CdTx positivity were community versus hospital acquisition [odds ratio (OR), 5.49; 95% confidence interval (CI), 2.52–11.95; P = 0.0001], presence of IBD (OR, 21.5; 95% CI, 8.65–53.44; P = 0.0001), PPI use (OR, 4.53; 95% CI, 1.97–10.43; P = 0.0001), immunosuppressive drug use (OR, 4.1; 95% CI, 2.01–8.3; P = 0.0001), and use of quinolone group of antibiotics (OR, 5.95; 95% CI, 1.92–18.46; P = 0.001). Female sex (OR, 1.23; 95% CI, 0.65–2.31; P = 0.52), type 2 diabetes (OR, 0.6; 95% CI, 0.24–1.5; P = 0.259), malignancy (OR, 0.42; 95% CI, 0.14–1.3; P = 0.186), ICU follow-up (OR, 0.32; 95% CI, 0.06–1.62; P = 0.276), a hospital stay >14 days (OR, 2.4; 95% CI, 0.55–10.45; P = 0.311), cephalosporin use (OR, 1.97; 95% CI, 0.69–5.62; P = 0.199), β-lactam/β-lactamase inhibitor use (OR, 0.84; 95% CI, 0.27–2.63; P = 0.772), and carbapenem use (OR, 0.47; 95% CI, 0.13–1.64; P = 0.229) were not associated with CdTx positivity. Antibiotic use was a protective risk factor (OR, 0.09; 95% CI, 0.01–0.78; P = 0.01) and presence of IBD was an independent risk factor (OR, 6.8; 95% CI, 1.5–30.08; P = 0.01) in community-acquired group compared with nosocomial group (OR, 0.09; 95% CI, 0.01–0.78; P = 0.01) [Table 2].

Multivariate logistic regression analysis revealed that the presence of IBD, PPI use, preceding antibiotic use, and use

Table 1: Univariate analyses of CdTx positivity and risk factors

	CdTx-positive *n*=78 (50%)	CdTx-negative *n*=78 (50%)	*P*	OR (95%CI)
Sex, *n* (%)				
Female	41 (52.6)	45 (57.7)	0.52	1.23 (0.65-2.31)
Male	37 (47.4)	33 (42.3)		
Age, mean±SD	41.3±16.3	51.12±20.16	0.001*	
Age groups (years), *n* (%)				
18-28	17 (21.8)	12 (15.4)	0.05*	
29-38	22 (28.2)	14 (17.9)		
39-48	17 (21.8)	12 (15.4)		
49-58	8 (10.3)	10 (12.8)		
59-65	7 (9)	9 (11.5)		
>65	7 (9)	21 (26.9)		
Presentation, *n* (%)				
Nosocomial	11 (14.1)	37 (47.4)	0.0001*	5.49 (2.52-11.95)
Community-onset	67 (85.9)	41 (52.6)		
Length of hospital stay, median (IQR)	19 (13-24)	15.5 (5.75-30.75	0.245	
Length of hospital stay	11/78	37/78		
<14 days, *n* (%)	3 (27.3)	18 (48.6)	0.304	2.5 (0.57-11.04)
>14 days, *n* (%)	8 (72.7)	19 (51.4)		
ICU follow-up, *n* (%)	2 (25)	6 (75)	0.276	0.32 (0.06-1.62)
IBD, *n* (%)	53 (67.9)	7 (32.1)	0.0001*	21.5 (8.65-53.44)
Ulcerative colitis	38 (48.7)	6 (7.7)		
Crohn's disease	9 (11.5)	1 (1.3)		
Previous antibiotic use,** *n* (%)	39 (50)	36 (46.2)	0.631	1.17 (0.62-2.18)
Cephalosporin group, *n* (%)	11 (14.1)	6 (7.7)	0.199	1.97 (0.69-5.62)
β-Lactam/β-lactamase inhibitor combination, *n* (%)	6 (7.7)	7 (9)	0.772	0.84 (0.27-2.63)
Carbapenem group, *n* (%)	4 (5.1)	8 (10.3)	0.229	0.47 (0.13-1.64)
Quinolone group, *n* (%)	19 (24.4)	4 (5.1)	0.001*	5.95 (1.92-18.46)
Previous PPI use, *n* (%)	29 (37.2)	9 (11.5)	0.0001*	4.53 (1.97-10.43)
Immunosuppressive therapy, *n* (%)	40 (51.3)	16 (20.5)	0.0001*	4.1 (2.01-8.3)
Type 2 diabetes, *n* (%)	9 (11.5)	14 (17.9)	0.259	0.6 (0.24-1.5)
Malignancy, *n* (%)	5 (6.4)	11 (14.1)	0.186	0.42 (0.14-1.3)

CdTx: *Clostridium difficile* toxin; OR: Odds ratio; CI: Confidence interval; SD: Standard deviation; IQR: Interquartile range; ICU: Intensive care unit; IBD: Inflammatory bowel disease; PPI: Proton pump inhibitor, *$P \leq 0.05$ was considered statistically significant, **Patients who used antibiotics in last 3 months

Table 2: Univariate analyses of community-acquired and nosocomial CDI

	Community-onset *n*=55 (84.6%)	Nosocomial *n*=10 (15.4%)	*P*	OR (95% CI)
Sex, *n* (%)				
Female	27 (49.1)	6 (60)	0.73	1.5 (0.4-6.13)
Male	28 (50.9)	4 (40)		
Age groups, *n* (%)				
18-28	15 (27.3)	1 (10)	0.003*	
29-38	16 (29.1)	0		
39-48	15 (27.3)	1 (10)		
49-58	3 (5.5)	3 (30)		
59-65	3 (5.5)	2 (31)		
>65	3 (5.5)	3 (30)		
Presence of IBD, *n* (%)	41 (74.5)	3 (30)	0.01*	6.8 (1.5-30.08)
Previous antibiotic use,** *n* (%)	25 (45.5)	9 (90)	0.01*	0.09 (0.01-0.78)
Previous PPI use, *n* (%)	22 (40)	4 (40)	1	1 (0.25-3.95)
Immunosuppressive therapy, *n* (%)	29 (52.7)	4 (40)	0.5	1.6 (0.42-6.64)
Malignancy, *n* (%)	2 (3.6)	2 (31)	0.1	0.15 (0.01-1.22)

OR: Odds ratio; CI: Confidence interval; IBD: Inflammatory bowel disease; PPI: Proton pump inhibitor, *$P \leq 0.05$ was considered statistically significant, **Patients who used antibiotics in last 3 months

of quinolone group of antibiotics were independent risk factors for CdTx positivity (OR, 67.1; 95% CI, 17.4–258.6; OR, 9.3; 95% CI, 2.9–29.3; OR, 3.9; 95% CI, 1.1–13.3; and OR, 4.8; 95% CI, 1.08–21.7, respectively) [Table 3].

DISCUSSION

We investigated the effects of specific risk factors for CdTx positivity in outpatients and inpatients in whom diarrhea developed during hospital stay, in Bezmialem Vakif University Hospital. Presence of risk factors such as IBD, PPI, and immunosuppressive drug use was found to be associated with toxin positivity, consistent with the previous studies. However, previous antibiotic use and prolonged hospital stay (>14 days) were not associated with toxin positivity in our study contrary to the literature.[11-13] Use of only quinolone antibiotics was associated with toxin positivity. A recent study demonstrated the association of use of the fluoroquinolones with toxin positivity. Fluoroquinolone-resistant strains were detected in CDI epidemics in Canada, the United States, and Europe especially after 2003.[14,15] We could not investigate the effects of strains, because genetic analyses could not be carried out.

Risk factors were compared in community-acquired and nosocomial CDIs. Recent studies demonstrated that community-onset CDI could develop in patients who do not have well-known risk factors and are not on antibiotics, contrary to previous studies, which reported CDI to develop in older, hospitalized, and antibiotic using patients. Incidence of community-acquired CDI was 29% in a study from Australia[16] and 45% in another report,[6] while it was 85.9% in our study, in which the incidence and the IBD ratio were higher.[6] Studies showed that IBD incidence was higher in developed countries compared with developing countries. However, this result may be ascribed to the fact that studies in developed countries were mostly prospective and population-based, whereas the studies in developing countries were mostly retrospective and hospital-based.[17] Incidence may be higher than what was reported in developing countries because population-based epidemiologic data are inadequate. Therefore, population-based prospective studies may be needed to determine the incidence of IBD in developing countries. In our study, high incidence of IBD in community-acquired CDI may be ascribed to the increase in IBD incidence. Association of IBD with CDI is vague. Although several studies advocate the role of CDI in IBD development, the mechanisms are not clear.[18] Patients with IBD are at risk for CDI because of administration of steroids, immunomodulating therapies, PPIs, antibiotics, and following changes in fecal microbiota. In addition, frequent hospital admissions and medical interventions may play a role in CDI development in patients with IBD.[18,19]

Community-onset CDIs were demonstrated to occur in younger patients who do not have chronic diseases (such as malignancies) and are not on antibiotics, in studies comparing community-onset and nosocomial infections.[6,16] Studies define different time spans for antibiotic use before CDI. For example, in one study the time span was last

Table 3: Multivariate regression analyses of risk factors for CdTx positivity

	Odds ratio	95% CI	*P*
Presence of IBD	67.1	17.4-258.6	0.0001*
PPI use	9.3	2.9-29.3	0.0001*
Previous antibiotic use**	3.9	1.1-13.3	0.02*
Quinolone group antibiotic use	4.8	1.08-21.7	0.03*

CdTx: *Clostridium difficile* toxin; CI: Confidence interval; IBD: Inflammatory bowel disease; PPI: Proton pump inhibitor. *$P \leq 0.05$ was considered statistically significant, **Patients who used antibiotics in last 3 months

30 days, whereas it was 90 days in another. Antibiotic use was negative in 60% in the former and 45.7% in the latter.[20,21] However, Deshpande *et al*. demonstrated in their meta-analysis that antibiotic use in community-acquired CDI was seven-fold higher. Antibiotic use was significantly higher in community-acquired cases compared to nosocomial cases in our study.

In our study, toxin positivity was not associated with increased age (especially >65 years) contrary to several previous studies.[22] This result may be due to higher incidence of IBD among younger individuals in our subgroup analyses. Although increased age seems to have a negative effect on toxin positivity in our study, this should not be inferred as a general rule.[23]

IBD is accepted as a risk factor for CDI in multivariate analyses in most studies. Although IBD was the most important risk factor in our study, other studies found antibiotic use in the last 90 days or last 30 days as the most important risk factor.[20,21,24,25]

CDI incidence was found to be increased with quinolone use in recent studies, whereas in earlier studies beta-lactam antibiotics were thought to be responsible for CDI.[26] Quinolones were associated with increase in the incidence of CDI in our study, consistent with the literature.

PPIs inhibit gastric acid secretion, so the environment becomes suitable for the overgrowth of *C. difficile* spores and germination.[27] Some studies revealed the association of PPI use with toxin positivity.[16] PPI use was associated with toxin positivity in our study, but not with CDI infection. CDI development in toxin-positive patients could not be elucidated. In a meta-analysis, the authors demonstrated a significant association of PPI use with CDI, but they reported the heterogeneity and the bias of the studies in the same article. They focused on other studies with contrary results and the need for well-designed prospective studies investigating the association of PPI use with CDI.[28]

Other studies found the association of prolonged hospital stay (>15 days) with toxin positivity, contrary to our study.[25]

We encountered toxin positivity mostly in outpatients. Previous epidemiological studies demonstrated toxin positivity in inpatients more than in outpatients. However, incidence in outpatients is increasing in recent studies. In our patient population, IBD and immunosuppressive therapy were common in outpatients, different from the clinical presentation after antibiotic use. These were in the high-risk group because they had frequent hospital admissions and colonoscopies. However, antibiotic use was a prominent risk factor in patients who did not have IBD.

We used the enzyme immunoassay (EIA) method, which has a sensitivity and specificity of 65%–85% and 95%–100%, respectively, in our study. The EIA method is the most common method in clinical studies owing to its easy and quick applicability.[9] However, low specificity of the method remains a disadvantage. Limitations of this study include diagnosing with single method, absence of a toxigenic culture, and not detecting the toxigenic strain by molecular methods.

In their updated guidelines, Infectious Diseases Society of America and Society for Healthcare Epidemiology of America recommend oral vancomycin and fidaxomicin in primary treatment of nonsevere CDI and metronidazole in the alternative treatment. In severe and fulminant CDI, only vancomycin and fidaxomycin are recommended. Fecal microbiota transplantation (FMT) with antimicrobial treatment is recommended in recurrent CDI especially in individuals with greater than or equal to two attacks.[29] Studies showed that factors affecting the success of the FMT could be routes of delivery, number of infusions, and faecal dosage. They also emphasized the necessity of individualized FMT scheme for each patient.[30]

In conclusion, old age, antibiotic use, and hospitalization were the most important risk factors for CDI in previous studies. However, in recent studies, CDI was demonstrated to be more frequent in younger individuals who did not have a history of hospitalization but had an underlying disease such as IBD. In our study, we showed the change in the epidemiological data with prominence of underlying diseases such as IBD. In the light of novel studies, CDI should be kept in mind for differential diagnosis in patients suffering from diarrhea and underlying IBD.

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Conflicts of interest

There are no conflicts of interest.

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