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Original Article

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Lack of Association Between the Clinical Outcome of *Clostridium difficile* Infection and Current Steroids Use

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Abstract

Background: The purpose of this study was to compare the outcome of *Clostridium difficile* infection (CDI) in patients on systemic steroids for various indications to patients not on steroids in term of disease severity, and associated morbidity and mortality.

Methods: We retrospectively reviewed records of all patients with CDI at our hospital from January 2011 to December 2016. Patients were evaluated for baseline characteristics, comorbidities, medications, disease severity, disease-related length of stay (LOS) from the diagnosis of CDI to discharge, need for surgical intervention, and disease-related mortality. Based on systemic steroids use, patients who were using steroids for different indications constituted the study population, and those with no steroids use were clustered as a control group.

Results: Of the 258 patients included, males were 127 (49%). Severe and severe-complicated CDI developed in 21/63 (33.3%) and 1/63 (1.6%) of patients on steroids (average daily dose of 20 mg), and in 73/195 (37.4%) and 5/195 (2.6%) of patients with no steroids use (P = 0.56 and P = 0.66, respectively). Surgical intervention was not required in the steroids group and 5/195 (2.7%) of patients not on steroids underwent bowel surgeries (P = 0.38). Mean LOS (days) was 11.6 ± 1.5 in the steroids group and 10.4 ± 0.7 in the no-steroids group (P = 0.4). CDI-related mortality occurred in 9/63(14.3%) of patients on steroids, and in 15/195 (7.7%) of patients not on steroids (P = 0.12; odds ratio (OR): 2; 95% confidence interval (CI): 0.8 - 4.8).

Conclusion: There was no significant difference in the severity of CDI, need for surgical interventions, disease-related LOS and mortality in systemic steroids users compared to patients not on steroids.

Keywords: *Clostridium difficile*; Steroids

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Introduction

Clostridium difficile (*C. difficile*) is a toxin-producing, spore-forming, gram-positive anaerobic bacillus that causes a spectrum of manifestations ranging from asymptomatic carriage to fulminant disease [1, 2].

In 2011, an estimated 453,000 cases of *C. difficile* occurred in the United States, and 29,300 patients died [3]. The incidence was higher in women, whites, and in individuals who were 65 years old or older than in those less than 65 years old [4].

Clostridium difficile infection (CDI) is defined as the acute onset of diarrhea with documented toxigenic *C. difficile* or its toxin and no other documented cause for diarrhea [5]. The diagnosis of CDI is established through a positive laboratory stool test for *C. difficile* toxins or *C. difficile* toxin gene. Real-time PCR tests detect one or more genes specific to toxigenic strains and are highly sensitive and specific [6-10].

Mild to moderate disease is defined as either diarrhea as the only symptom, or diarrhea without additional symptoms and signs meeting the definition of severe or complicated CDI. Severe disease is associated with hypoalbuminemia (serum albumin < 3 g/dL) and either a white blood cell (WBC) count ≥ 15,000 cells/mm^3 or abdominal tenderness without criteria of complicated disease. Severe complicated disease requires presence of at least one of the following: fever ≥ 38.5 °C, ileus, or significant abdominal distention, WBC ≥ 35,000 cells/mm^3 or < 2,000 cells/mm^3, serum lactate levels > 2.2 mmol/L, admission to intensive care unit, hypotension with or without required use of vasopressors, changes in mental status, or any evidence of end organ failure [10].

Patients with mild-to-moderate CDI should be treated with metronidazole 500 mg orally three times per day for 10 days unless they are intolerant or allergic to metronidazole or during pregnancy or breastfeeding. Patients with severe disease should be treated with vancomycin 125 mg four times daily for 10 days, and oral vancomycin (125 mg four times per day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice in patients with severe and complicated disease [10].

Glucocorticoids have inhibitory effects on a broad range of immune responses. Steroids are also among the most potent anti-inflammatory and immunosuppressive agents and can be used to reduce inflammation [11-13]. Currently, studies also focus on other therapeutic measures such as vaccination, toxin

Table 1. Baseline Characteristics of Patients With CDI

	CDI in patients on steroids	CDI in patients not on steroids	P-value
Age (years)	65.9 ± 1.7	65.08 ± 1.2	0.68
Gender	Males: 29/63 (46%)	Males: 98/195 (57%)	0.56
Race			
Black	18 (28.6%)	57 (29.2%)	0.92
White	38 (60.3%)	110 (56.4%)	0.59
Others	7 (11.1%)	28 (14.4%)	0.51
Comorbidities			
Diabetes mellitus	22 (34.9%)	100 (51.3%)	0.16
End-stage renal disease/hemodialysis	7 (11.1%)	32 (16.4%)	0.38
Immunosuppression	16 (25.4%)	31 (15.9%)	0.09
Gastric acid suppression	4 (6.4%)	22 (34.9%)	0.31

binding immunoglobulins, alternative antibiotics and altering gut flora with probiotics and fecal microbiota transplantation (FMT) [14-18].

In this study, we examined the association between the ongoing use of systemic steroids and the clinical outcome of CDI in a single-center retrospective cohort.

Materials and Methods

Setting

This study was conducted at an urban teaching acute care healthcare facility in northeastern USA. The study was approved by the Institutional Review Board (IRB) of the facility.

Study design and subjects

We retrospectively reviewed records of all patients with a documented diagnosis of CDI at our hospital from January 1, 2011 to December 31, 2016. Electronic charts of 355 patients admitted to our center with presumptive CDI were identified. Of these, 258 patients were found to have a confirmed diagnosis of CDI based on PCR tests for toxigenic *C. difficile* in stool samples.

Patients were evaluated to determine age, gender, race, medications including systemic steroids use, comorbidities, disease severity, disease-related length of stay (LOS), need for surgical interventions, and disease-related mortality. Based on the documented systemic use of steroids, patients who were using steroids for different indications (57 patients for chronic obstructive pulmonary disease/asthma, three patients for rheumatologic diseases, two patients for replacement therapy and one post-transplant patient) constituted the study population, while those not on steroids were clustered as a control group. Both groups received CDI treatment based on current national guidelines and there were no management differences within the same severity class between the two groups.

The severity of CDI was determined by the CDI severity scoring system based on the guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections from the American College of Gastroenterology [10].

Statistical analysis

Interval data were tested for fit-to-normality by the D'Agostino-Pearson omnibus normality test. Data which did not distribute normally were subjected to the appropriate non-parametric methods; otherwise parametric methods for group-wise comparisons were used. Normally distributed interval data were expressed as mean ± standard deviation (SD), and non-normally distributed interval data were presented as median and interquartile range (IQR). Univariate categorical data were evaluated for significance by using the Chi-squared test or Fisher's exact test as appropriate.

Because of the retrospective nature of the study, the odds ratio (OR) and 95% confidence interval (95% CI) were used as the measure of effect size. All inferences regarding statistical significance were based on a P-value < 0.05 on a two-sided basis. Analyses were performed using Prism® software (GraphPad Corp., San Diego, CA) or SPSS® version 22.0 (IBM Corp., Armonk, NY).

Results

Demographic and baseline characteristics

Of the 258 patients included, we identified 63 cases in the steroids group, and 195 cases of CDI cases in the non-steroids group. Baseline patients' characteristics are illustrated in Table 1.

Outcomes

The study did not show a statistical difference in the severity

Table 2. Outcome of CDI Among the Study Groups

Outcome	CDI in patients on steroids	CDI in patients not on steroids	OR (95% CI)	P-value
Disease severity				
Mild-moderate	41 (65.1%)	117 (60%)	1.24 (0.7 - 2.2)	0.47
Severe	21 (33.3%)	73 (37.4%)	0.84 (0.5 - 1.5)	0.56
Severe-complicated	1 (1.6%)	5 (2.6%)	0.61 (0.07 - 5.3)	0.66
Need for surgical intervention	0/63 (0.0%)	5/195 (2.6%)	0.27 (0.01 - 5.0)	0.38
Length of stay (days)	11.6 ± 1.5	10.4 ± 0.7		0.4
Mortality	9/63 (14.3%)	15/195 (7.7%)	2 (0.8 - 4.8)	0.12

pattern of CDI between the two groups. Only five patients in the non-steroids group underwent surgery and no one in the steroids group needed operative management (P = 0.38; OR: 0.27; 95% CI: 0.01 - 5.0). CDI-related mortality was encountered in nine patients in the steroids group and 15 patients in the non-steroids group. Mortality differences were not statistically significant between the two groups (P = 0.12; OR: 2; 95% CI: 0.8 - 4.8). Table 2 summarizes the different outcomes in these two groups.

Discussion

The results of this retrospective cohort study show that the severity of CDI is not affected by ongoing steroids use. Although, corticosteroids have remained the mainstay of therapy for acute flare-ups of inflammatory bowel disease [3], there is still no potential role of steroids in the treatment of *C. difficile*-associated diarrhea (CDAD). As a preventive measure, Wojciechowski et al examined the impact of corticosteroid use on the incidence of CDAD in patients receiving antibiotic treatment for respiratory infections. The use of corticosteroids was associated with a decreased incidence of CDAD (OR: 0.12; 95% CI: 0.006 - 0.95) [19].

Timely surgical consultation is essential in patients with refractory or fulminant colitis and subtotal colectomy with end ileostomy remains the standard operation for fulminant CDI [20]. As there was no statistical difference in the severity of CDI among study population, differences in the surgical interventions rates were similarly not statistically significant.

The study also revealed that steroids use did not affect the LOS in patients with CDI. Campbell et al reported renal impairment, advanced age, and cancer were associated with significantly longer LOS among hospital-onset CDI patients [21, 22]. Stevens et al studied the excess LOS attributable to CDI in acute care hospitalizations, and found that, CDI significantly contributes to the overall LOS. The greatest impact on LOS occurred among patients with severe CDI. The excess LOS for mild-to-moderate CDI was 0.75 days (95% CI: 0.59 - 0.89), and for severe CDI, it was 4.11 days (95% CI: 3.90 - 4.32) [23]. Intensive care unit (ICU) patients with CDI in particular have a greater adverse outcome. Patients with *C. difficile* in the ICU experienced higher mortality and longer LOS within the hospital [24]. ICU patients also experienced 3.4 times the odds of mortality (95% CI: 1.8 - 6.2) [24]. In comparison, a multicenter retrospective cohort study found CDI acquired in the ICU is associated with an increase in length of ICU and hospital stay but not with any difference in ICU or hospital mortality [25].

In our study, there was no difference in mortality rates among patients with CDI on steroids and patients not on steroids. Bhangus et al examined overall 30-day mortality among patients with CDI [26]. In this study, 30-day mortality was higher among medical patients (46%) and orthopedic patients (37%) compared with general surgical patients (13%, P = 0.006) [26]. Among a Medicare beneficiary cohort of patients, CDI was associated with greater inpatient mortality, 30-day mortality, longer LOS and higher rates of 30-day hospital readmissions [27]. A study of the elderly population (age > 65 years) found a significant excess mortality of 11.5% at 7 days, 26.2% at 30 days, 38.1% at 90 days and 41.4% at 180 days [28].

There were few limitations with this study. Although the study has adequate sample size, it is retrospective nature and being a single center work limits its applicability to patients in other hospitals/facilities.

Conclusions

In this study, since we found no association between the ongoing use of systemic steroids and the clinical outcome for CDI, we suggest that prescribed steroids for chronic diseases can be continued throughout the course of CDI.

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Financial Disclosures

None.

Conflicts of Interest

None.

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