

# Risk Factors for Relapse and Mortality of *Clostridium Difficile*-Associated Diarrhea

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## Abstract

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**AIM:** The aim of the present paper was to identify prognostic factors for relapse and mortality in patients with hospital-acquired infections caused by *Clostridium difficile*.

**MATERIAL AND METHODS:** This study included 133 patients with healthcare facility-associated disease caused by *C. difficile*. The medical records of all patients with their clinical history and laboratory data were analyzed.

**RESULTS:** Patients with one onset of disease were 105 (78.9%), 28 (21.1%) experienced a relapse and seven (5.2%) patients not survived infection. The average age in our patients was over 65 years (64.5 years in the survived patients and 78.8 in patient who died,  $p = 0.01$ ). All of patients had received antibiotic treatment (cephalosporins – 83.4%, aminoglycosides – 21.5% and penicillins – 20.3%) and 40.6% of patients received acid-reducing therapy. There was no difference between patients with one onset of disease/patients with relaps; and survived/died in number of administered antibiotics, duration of administration, administration of acid-reducing treatment or length of hospital stay ( $p > 0.05$ ). CRP levels were significantly higher in the group of patients who died compared with recovered ( $p < 0.001$ ).

**CONCLUSION:** *C. difficile*-associated diarrhea is a common nosocomial disease with high relapse, and significant mortality rate particularly in the elderly.

## Introduction

*Clostridium difficile* (*C. difficile*) is an anaerobe, Gram positive, sporogenic bacterium found in soil and intestinal tract of humans and animals. It is excreted by host through stool and the infection develops through activation of spores that are present in digestive tract or through fecal-oral pathway, by ingestion of spores found on surfaces or hands of health care staff in hospital settings [1]. *C. difficile* produces at least two different toxins, toxin A and/or toxin B, both of which are cytotoxic and enteropathogenic and cause diarrhea and enterocolitis [2]. The disease usually develops after administration of antibiotics that disturb host's normal gut flora [3]. The disease may occur sporadically, but in the past few years it became epidemic in hospitals and other public health care facilities. With appropriate treatment, the disease mostly ends by restitution to health; however, recurrence may occur, while in most severe cases, death may occur as well [1, 3].

The aim of this paper was to analyze and compare different types of clinical course of *C. difficile* infection, and to try to identify risk factors that might influence relapse or mortality.

## Methods

### Patients

This retrospective study included inpatients diagnosed with *C. difficile*-associated diarrhea (CDAD) from January 1, 2009 to December 31, 2012. In all patients, the disease was identified at different departments of General Hospital Subotica, Serbia from which all of them were transferred to the Infectious Disease Department of the same hospital.

The evaluated data include age, gender and date of diagnosis. In all patients, the analyzed data included onset of complaints, duration of hospital stay, number and time of administration of antibiotics, treatment with proton pump inhibitors (PPIs) and H2

receptors agonists, patient characteristics as risk factors (underlying illness-comorbidities, surgical procedures, endoscopy), body temperature, number and appearance of stools over 24-hour period, white blood cells (WBC) count, and C-reactive protein (CRP) levels. The above mentioned data were obtained from the medical records. In accordance with primary objective of this study, patients were classified into three groups: (1) those who responded to treatment without clinical relapse (2) patients with relapse of disease, and (3) patients who died due to disease.

### Definition

Healthcare facility-associated disease: (1) the presence of diarrhea, defined as passage of 3 or more unformed stools in 24 or fewer consecutive hours; (2) patients who received antibiotics and in whom symptoms occurred at least 48 hours after hospital admission, (3) patients with positive laboratory finding of *C. difficile* A toxin and/or B toxin in stool [4].

### Testing for *C. difficile* Toxins

The presence of *C. difficile* toxins in stool was performed using ELISA-RIDASCREEN Toxin A/B test (R-Biopharm AG, Germany).

### Statistical Analysis

Categorical variables are presented as absolute and relative frequencies, whereas continuous variables are summarized as mean  $\pm$  SD. Chi-square, Z-test and Student's t-test were used for comparison of categorical and continuous variables, respectively. The rejection of the null hypothesis was set at 5% ( $P < 0.05$ ).

## Results

The study included 133 patients, 67 (50.3%) males and 66 (49.6%) females. The average patient age was 65.3 years (range: 24.2-89.1 years). In 105 (78.9%) patients diarrhea did not recur and 28 (21.1%) patients experienced a relapse. Seven (5.2%) patients died (in the group of one-episode *C. difficile* infection five and in the group with relapse two), six of seven patients who died due to toxic megacolon (85.7%). Details concerning the hospitalization treatment, comorbidities, surgical and gastrointestinal procedures are presented in Table 1. All of the patients were treated with antibiotics. Metronidazole as monotherapy was associated with CDAD in one patient, while it was given in combination with other antibiotics in nine patients. Altogether, 33.1% of the patients were treated with more than one antibiotic.

**Table 1: Some risk factors in 133 patients with CDAD.**

Treatment and risks for CDAD	Number of patients (%)
Type of antibiotics	
Cephalosporins	111 (83.4)
Aminoglycosides	28 (21.0)
Penicillins	27 (20.3)
Metronidazole	10 (7.5)
Macrolides	9 (6.7)
Fluoroquinolones	7 (5.2)
Other	5 (3.7)
Number of antibiotics	
1	89 (66.9)
2	29 (21.8)
3	10 (7.5)
4	2 (1.5)
>4	3 (2.2)
Acid-reducing treatment	54 (40.6)
Risk factors	
Post-surgery	37 (27.8)
Cancer	28 (21.0)
Diabetes mellitus	22 (16.5)
Endoscopy	10 (7.5)
Inflammatory bowel disease	4 (3.0)

Table 2 shows toxins in stool, clinical characteristics and presentation in patients with *C. difficile* infection.

**Table 2: Clinical and laboratory findings in 133 patients with CDAD.**

Clinical and laboratory findings	Number of patients (%)
Symptoms and physical signs	
Mucus in stool	30 (22.5)
Rectal bleeding	4 (3.0)
Edema/ascites	27 (20.0)
Toxic megacolon	9 (6.7)
Toxins in stool	
Toxin A/B	126 (94.7)
Toxin A	3 (2.2)
Toxin B	4 (3.0)

Analysis that evaluated the influence of the various risk factors on patients' on recurrence and mortality is shown in Tables 3 and 4.

**Table 3: Clinical and biochemical factors affecting recurrence of *C. difficile* infection.**

	Initial CDAD (No 105)	Recurrent Disease (No 28)	P-value
Gender male/female	52/53	15/13	$p > 0.05$
Years ( $\pm$ SD)	63.5 $\pm$ 14.9	68.4 $\pm$ 12.2	$p > 0.05$
Acid-reducing treatment (%)	45 (42.8)	9 (33.3)	$p > 0.05$
Number of antibiotics ( $\pm$ SD)	1.6 $\pm$ 1.0	1.3 $\pm$ 0.6	$p > 0.05$
Duration of treatment	10.9 $\pm$ 6.3	11.3 $\pm$ 8.0	$p > 0.05$
Duration of hospital stay	13.4 $\pm$ 7.7	12.6 $\pm$ 8.5	$p > 0.05$
CRP (U/L)	80.3 $\pm$ 78.8	101.2 $\pm$ 91.8	$p > 0.05$
WBC ( $\times 10^9/L$ )	13.1 $\pm$ 8.2	14.0 $\pm$ 6.1	$p > 0.05$
Number of stools	6.78 $\pm$ 4.4	8.5 $\pm$ 4.2	$p > 0.05$
Fever (%)	36 (34.3)	10 (35.7)	$p > 0.05$

CRP - C-reactive protein; WBC - white blood cells

There was no significant difference in clinical and biochemical factors between patients with one onset of disease and patients who had relapse ( $p > 0.05$ ). In contrast to other characteristic, only older age of patients ( $p = 0.01$ ) and increased CRP levels ( $p < 0.001$ ) were associated with high mortality rate.

## Discussion

Because of its mild clinical course without complications, CDAD has traditionally been considered to be adverse effect of antibiotic therapy [5]. In the period 2004-2008, numerous reports from USA, Canada and Europe changed perception of infection by this anaerobic bacterium that became

more aggressive, refractory to standard treatment, and with higher numbers of relapses, severe cases and higher mortality rates [6-10]. Until now, two reports have been published on *C. difficile* in Serbia: Stojanovic and Kocic presented the case of CDAD in patient after cholecystectomy, while the other was an epidemiological study by the same authors who found presence of *C. difficile* in 4/100 hospitalized patients with diarrhea [11, 12].

**Table 4. Clinical and biochemical factors affecting mortality of *C. difficile* infection**

	Survived (No 126)	Died (No 7)	P-value
Gender male/female	65/61	2/5	p>0.05
Years (±SD)	64.5 ± 14.5	78.8 ± 9.0	p=0.01
Acid-reducing treatment (%)	51 (40.47)	3 (42.8)	p>0.05
Number of antibiotics (±SD)	1.5 ± 0.9	1.5 ± 0.5	p>0.05
Duration of treatment	10.9 ± 6.6	10.5 ± 3.6	p>0.05
Duration of hospital stay	13.2 ± 7.8	10.7 ± 3.6	p>0.05
CRP (U/L)	85.7 ± 82.0	204.4 ± 11.5	p<0.001
WBC (x10 <sup>9</sup> /L)	13.69 ± 7.8	30.0 ± 30.9	p>0.05
Number of stools	7.9 ± 4.3	9.8 (5.0)	p>0.05
Fever (%)	43 (34.1)	3 (42.8)	p>0.05

CRP - C-reactive protein; WBC - white blood cells

Although administration of virtually any antibiotic may cause development of CDAD, it usually occurs after administration of cephalosporins, wide spectrum penicillin, clindamycin and fluoroquinolones [5, 13]. Metronidazole is rarely associated with this disease [14]. Combination of metronidazole and other antibiotics was associated with CDAD in 9 patients in this study (other antibiotics could have caused this multifactor disease in these patients, but metronidazole administration did not prevent it), while metronidazole alone was the only proven initiator of the disease in one patient.

Although the disease most commonly resolves with complete restitution to health, relapses occur in 20-25% of patients (even in >30% of cases for the new strain), while mortality rates range from 1-2.5% [15]. The relapse rate among patients in this study was similar (21.1%), while mortality rates were up to two times higher (5.2%) compared to those reported by Zilberberg et al. (2.3%) [16]. Dallal et al. found an increase in rate of fulminant life threatening colitis from 0% in 1990 to 3.2% in 2000 [17]. From those, 44 patients underwent subtotal or total colectomy with high mortality rate of 57%, while 20 patients died due to colitis. Toxic megacolon was the leading cause of death among patients in this study (6/7). Several risk or predictive factors for mortality have been described, such as old age, elevated WBC, prolonged antibiotic use of more than 4 weeks or pretreatment with three or more antibiotics [18, 19, 20]. In the present study only older age and high levels of CRP was identified as predisposing factor for mortality.

Previous studies have found numerous risk factors for relapse of CDAD, including older age, long hospital stays, and concomitant receipt of antacid medications, female gender, and additional antibiotics for treatment of other infections [21, 22]. Although our patients with relapse were on average older than those without relapse, there was no significant

difference between the two groups. Older age was identified as predisposing factor only for the most severe cases ending with death.

Although the mechanism of development of recurrent *C. difficile* infection is not entirely understood, Maroo and Lamont argued that recurrence is more likely to be caused by external re-infection by *C. difficile* through feco-oral pathway than by reactivation of primary infection [23]. Longer hospital stay of patients with CDAD might additionally expose patients to spores of *C. difficile*, thus increasing the risk of disease relapse. Among patients in this study, the length of hospital stay was not identified as risk factor for disease relapse. The group of Canadian scientists from Quebec found that recurrences occurred even less commonly in patients who were hospitalized for >30 days [24]. Same authors concluded that re-infection has minor significance and that the main cause of recurrence is relapse of the initial disease. Among patients from different groups within this study, there was no difference in length of antibiotic treatment or number of administered antibiotics. It is likely that the main factor influencing course of the disease is host's immunological response, while antibiotic treatment and contamination by spores from hospital environment are only prerequisites for development of the disease.

Administration of PPI, i.e. H<sub>2</sub> receptors agonists, is considered to be predisposing factor for both development of the infection and for relapse, although opinions of different authors on that matter may be conflicting [25, 26]. The United States Food and Drug Administration (FDA) have recently informed the public on possible association of *C. difficile* infection and administration of PPIs [27]. The mechanism of development of the disease has been explained by disruption of hydrochloric acid barrier, delayed gastric emptying and increased level of bile salts [28]. Among patients in this study, acid-reducing treatment was not identified as predisposing factor for recurrence or death. The group of authors from various countries used rigorous selection to perform meta analysis of 47 relevant studies and found very low quality evidence on association between PPIs and *C. difficile* infection [29]. This opinion has been confirmed by the *in vitro* experiment: it has been shown on hospitalized patients, from whom gastric aspiration was collected using gastric tube, that *C. difficile* spores were not destroyed by hydrochloric acid. Furthermore, no spores germination has been shown in gastric contents of patients who received PPIs [30].

This study had several limitations. Firstly, it was a retrospective study with relatively small number of subjects. Secondly, it did not include all patients, because certain number of patients developed disease after discharge and were treated at nursing homes from which no medical records were later available.

In conclusion, the CDAD is a significant cause of diarrhea syndrome among elderly inpatient population, but the number and duration of administered antibiotics, length of hospital stay, or acid-reducing treatment did not correlate with different types of clinical course of *C. difficile* infection. This study confirms that the hospital infection caused by *C. difficile* is present in our settings with significant rates of mortality and recurrence.

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