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The Role of Antibiotics in the Development of Pseudomembranous Colitis Caused by the Bacterium *Clostridium Difficile*

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ABSTRACT: The most common pathogen responsible for the development of pseudomembranous colitis is the bacterium *Clostridium difficile*. The gut microbiota has a protective role because it prevents the adhesion of pathogens to receptors on host cells. Materials and Methods**:** In this retrospective study, data from medical histories of the patient with confirmed *Clostridium difficile* infection, was hospitalized at the Clinic for Infection Diseases in the Clinical Centre of Sarajevo University.

RESULTS: Of all patients, 81.2% used antibiotics before the onset of symptoms. The largest number of antibiotics used were group β lactam antibiotics (46.9%), while from the group of other antibiotics, quinolones were used the most (45.5%). The largest number of patients experienced the first attack (89.1%). Metronidazole was the most common drug of choice for *Clostridium difficile* infection (81.3%). The combination of metronidazole and vancomycin was received in 15.6% of cases, and in 3.1% of cases.

CONCLUSIONS: Our study showed that pseudomembranous colitis developed in a small percentage in patients who had not used antibiotics at all before the onset of symptoms. In patients undergoing antibiotic therapy, the risk of developing *C. difficile* pseudomembranous colitis was slightly higher with β-lactam antibiotics than with other antibiotics.

KEYWORDS: antibiotics, pseudomembranous colitis, *Clostridium difficile*

I. INTRODUCTION

Pseudomembranous colitis (PMC) is a manifestation of severe colon disease usually associated with *Clostridium difficile* (*C. difficile*) infection, but there may be other etiological factors for the disease. The development of the disease is favored by a prolonged hospital stay, older age (over 65 years), and severe primary illness (comorbidities). Before using broad-spectrum antibiotics, PMC usually occurred in ischemic disease, obstruction, sepsis, uremia, and heavy metal poisoning [1, 2]. The entire gastrointestinal tract (GIT) is inhabited by microorganisms, predominantly bacteria. The majority of bacteria are found in the cecum and transversal colon, where the bacterial population range from around 10^{12} to 10^{14}/ml. Intestinal microflora plays a major role in the host defense, stimulates the production of IgA, and modulates local T-lymphocytes [3, 4], so that intestines, together with microbiota, form 70% of the human immune system [5].

C. difficile is a gram-positive, sporogenic, anaerobic bacterium. Almost 50% of newborns carry this bacterium asymptomatically during the first year of life, and only 3% of children older than two years and adults [4]. It is very easily transmitted in a hospital environment and found in 20-30% of hospitalized patients, and about one-third of them become ill [5]. *C. difficile* becomes pathogenic in situations of intestinal flora imbalance (dysbiosis), which usually occurs with the application of antibiotic therapy [6]. When broad-spectrum antibiotics are administered orally, they destroy the physiological flora of the intestine and inevitably lead to the development of intestinal infection. This is the reason that *C. difficile* endospores translate into vegetative forms, followed by uncontrolled growth of bacteria. *C. difficile* is generally a non-invasive bacterium because it does not enter the bloodstream from the colon. It remains in the lumen of the intestine where it produces toxins that cause the development of antibiotic-associated diarrhea [4, 6]. *C. difficile* also causes infectious diarrhea in the population, often without the use of antibiotics. Pathogenic strains of *C. difficile* have a so-called locus of pathogenicity, which contains genes encoding two toxins: the tcdA gene (*C. difficile* toxin A) and the tcdB gene (*C. difficile* toxin B).

Toxin A breaks down the compounds that hold the cells of the lining of the colon together, which triggers inflammation and allows for fluid loss. Toxin B directly kills colon cells and stimulates the formation of lesions that fuse into the characteristic pseudomembrane [5].Severe forms of diarrhea, often associated with intense inflammation and the formation of lesions in the colon, often develop in hospitalized patients taking antimicrobial drugs. It can be said that pseudomembranous colitis is a by-product of modern medicine because, before the use of antibiotics took on wide proportions, this disease occurred very rarely [4]. If bacteria resistant to applied antibiotics are present in the gut, they will multiply uncontrollably, which can result in severe enterocolitis (eg antibiotic-associated diarrhea caused by *C. difficile*) [7].

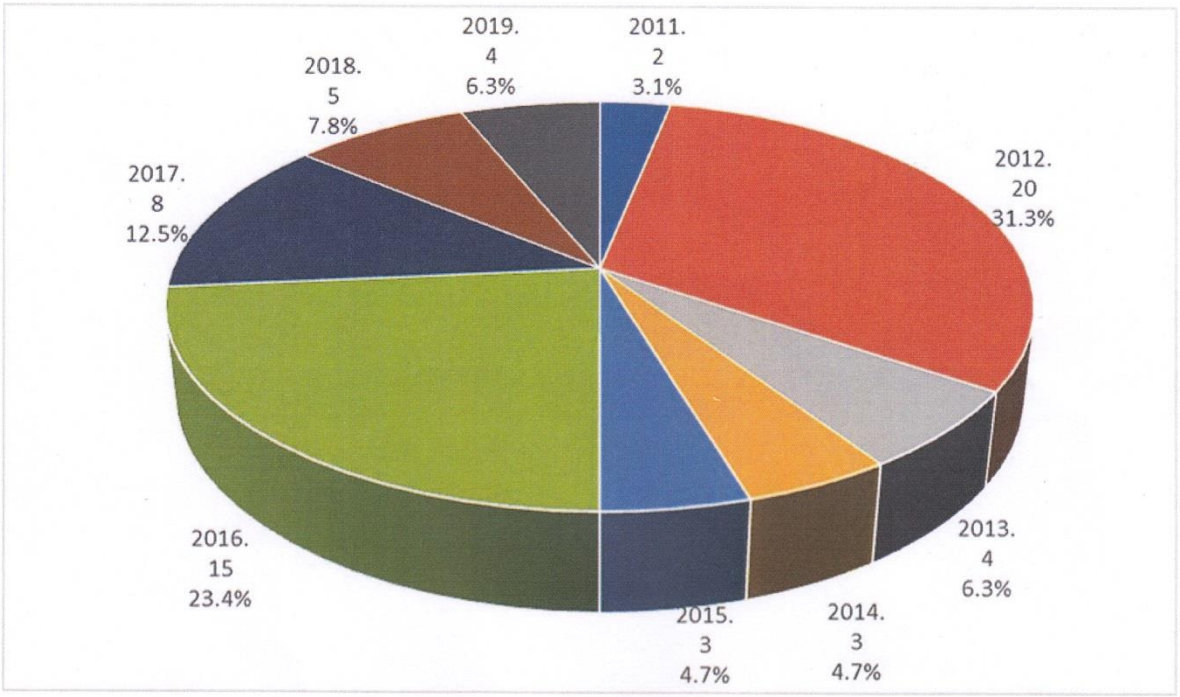
The clinical presentation of *Clostridium difficile* infection (CDI) may vary from an asymptomatic carrier to a fulminant form of the disease with toxic megacolon [8]. CDI symptoms may occur during antibiotic use or one month later, but usually, they occur within 3-9 days after antibiotic therapy [9]. All antibiotics present a risk of post-antimicrobial diarrhea/CDI. However, fluoroquinolones, clindamycin, and penicillins have the highest risk potency for post-antimicrobial CDI. Additional risk factors are age above 65, impaired immune system, comorbidities, previous infection with *C. difficile*, etc. [10]. An asymptomatic carrier represents a reservoir of infection that can contaminate the hospital or other environment. *C. difficile* is in the etiology of about 20% of cases of post-microbial diarrhea which represents the mild form of the disease and is characterized by more than 3 loose stools in 24h without general symptoms [11]. The infectious Diseases Society of America /IDSA/ and the Society for Healthcare Epidemiology of America /SHEA/ in 2017, issued new recommendations for the treatment for CDI in adults and children. The first step in treatment management is to assess the severity of the disease, and according to that to give a proper antibiotic treatment [12].Metronidazole is recommended only for mild/moderate first episode or when vancomycin or fidaxomicin is not available. Its use should be avoided especially in the elderly or people with developed CDI in irritable bowel disease. Vancomycin 500 mg 4 x 1 per os as well as metronidazole intravenously is recommended for patients with fulminant CDI form. Metronidazole is not recommended in relapses. If the patient previously used metronidazole, vancomycin per os is given. If the patient has previously used vancomycin, it should be used again but in a prolonged tapered regime, or fidaxomicin could be given instead. If the patient has more than one relapse, it could be treated with vancomycin, fidaxomicin, or fecal transplantation [12, 13].

II. MATERIALS AND METHODS

The study is retrospective, involving patients who were hospitalized at the Clinic for Infectious Diseases of the Clinical Center of the University of Sarajevo (KCUS) in a ten-year period (from 2011/01/01 to 2019/12/31). The study included only those patients with confirmed *C. difficile* infection. In the microbiological laboratory, all stool samples were tested with the *C. difficile* GDH Ag Rapid test, and then only positive samples were further tested with the Serazym *Clostridium difficile* toxin A+B test. Data obtained from medical records included the age and sex of the patient, the duration of hospitalization, information as to whether it was the first episode of the disease or recurrence, used antibiotic therapy prior to the onset of symptoms, and manner of use (orally or parenterally), treatment duration before the onset of symptoms, whether the therapy was administered in a clinic or in an outpatient setting, which therapy was prescribed at the clinic, the duration of therapy, and the outcome per patient. The results are presented in tables and graphs through an absolute and relative number of cases, arithmetic mean with standard deviation and value range, or median and interquartile ranges. The non-parametric chi-square test, the Ficher exact test, the Mann-Whitney test, and the Kruskal-Wallis test were used to test the differences between the observed groups.

III. RESULTS

The study included a total of 64 patients with a proven presence of *C. difficile* by Ag (GDH) and EIA (tox A and B) tests. In the ten-year period, the largest number of registered cases was recorded in 2012, 20 or 31.3% of them, followed by 2016, 15 or 23.4% of them, while the smallest number was recorded in 2011. where were only 2 or 3.1% (Graph 1).



Graph 1. Distribution of registered patients from 2011 to 2019.

Patients were divided into three groups depending on the antibiotics they used, namely the group that used β lactam antibiotics, the group that used other antibiotics, and those that did not use antibiotics at all before the symptoms began. The comparison of average age by observation groups shows that on average the oldest patients were using β lactams before the onset of symptoms with an average age of 73.6 ± 13.3 years (range 24-91 years), followed by patients using other antibiotics with an average age of 72.3 ± 13.8 years (range 35-92 years), and youngest patients who did not use antibiotics with an average age of 69.3 ± 13.9 years (range 42-87 years) with H = 1.253, p=0.534; p>0.05.Out of the total number of subjects, 64.1% (41 subjects) were males and 35.9% (23 subjects) were females. The analysis of sexual distribution by observation groups shows that men were more represented in all three groups, without statistically significant differences between groups p> 0.05 (Table 1).

Table 1. The comparison of categorical variables between groups

			Group			Total
			β laktams	Others	Not used	
Sex	Male	N	19	15	7	41
		%	63,3	68,2	58,3	64,1
	Female	N	11	7	5	23
		%	36,7	31,8	41,7	35,9
Total		N	30	22	12	64
		%	100,0	100,0	100,0	100,0

Out of the total number of patients, 18.8% did not use any antibiotics prior to the onset of symptoms. Out of the total number of patients, the most used antibiotic group was β lactam antibiotics (46.9%) and the group of other antibiotics (34.3%). In the group of other antibiotics, the most frequent were quinolone antibiotics (45.5%), and sulphonamides (18.2%), (Table 2).

Table 2. The comparison of categorical variables between groups according to antibiotics used before the onset of symptoms

			Grup		Total
			β laktams	Others	
Used antibiotics before symptoms onset	β laktams	N	30	0	30
		%	100,0	0,0	46,9
	Quinolones	N	0	10	10
		%	0,0	45,5	15,6
	Sulphonamides	N	0	4	4
		%	0,0	18,2	6,3
	Others	N	0	8	8
		%	0,0	36,4	12,5
	Not used	N	0	0	12
		%	0,0	0,0	18,8
Total		N	30	22	64
		%	100,0	100,0	100,0

The groups were compared according to whether they had the first episode or whether it was a recurrence. The first episodes were slightly less prevalent in the group of patients using β lactams (93.3%) than those using other antibiotics. Although recurrence is slightly higher (6.7%) in the group of β lactam antibiotics compared to other antibiotics (4.5%) (Table 3)

Table 3. A combination of categorical variables between groups depending on whether the first episode or recurrence

			Group		Total
			β laktams	Others	
First episode or recurrence	First episode	N	28	21	57
		%	93,3	95,5	89,1
	Recurrence	N	2	1	7
		%	6,7	4,5	10,9
Total		N	30	22	64
		%	100,0	100,0	100,0

$\chi 2$=0,105; ss=1; p=0,617

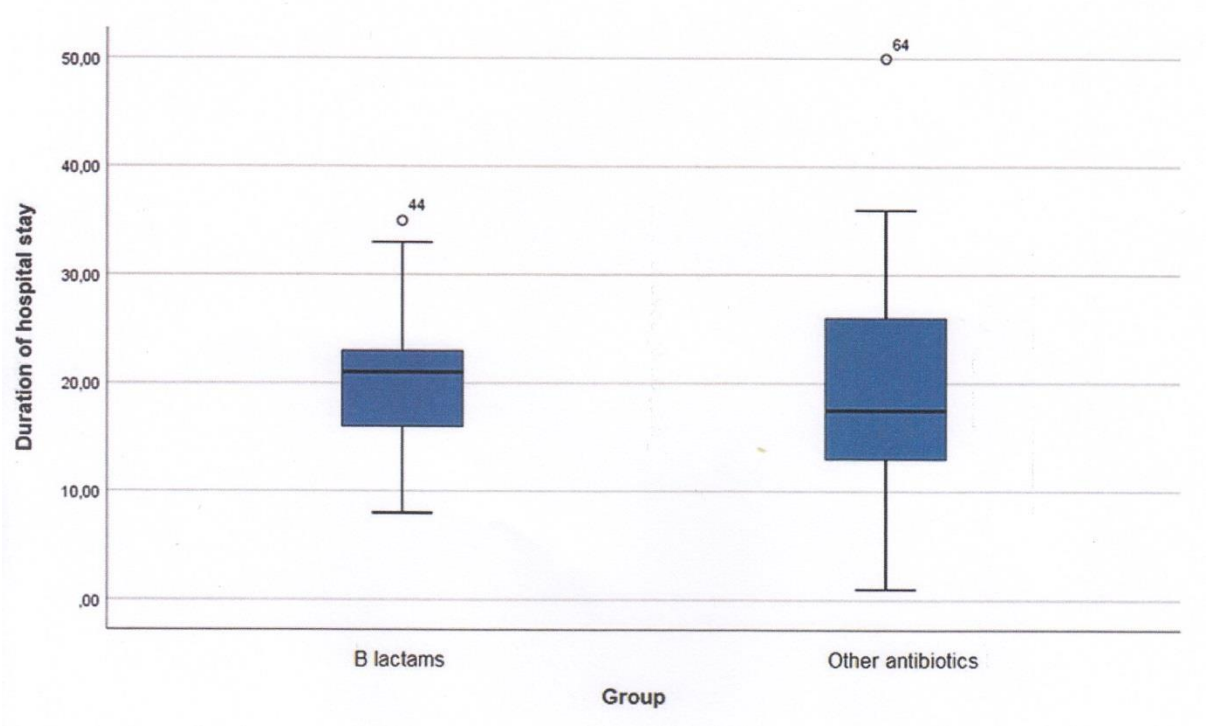
Patients from both groups were treated in an ambulance (outpatient basis) or hospital. Out of the total number of treated patients, 60% of them using β lactam antibiotics were treated in hospital conditions, while 81.8% using other antibiotics were treated in an ambulance. Out of the total number of patients, the most commonly used antibiotic in both groups was metronidazole, in 81.3% of cases, and no statistically significant difference was seen ($p > 0.05$). In the group of patients using β lactam antibiotics, there was the need to use combined therapy in 20% of the cases, as opposed to the group receiving other antibiotics (9.1%). The need for therapy did not have 9.1% of the cases from the group of other antibiotics (Table 4).

Table 4. The comparison of categorical variables between groups according to the ordinated antibiotic at the clinic

			Group		Total
			βlaktams	Others	
Ordinated antibiotics in the clinic for Infectious deseases	Metronidazole	N	24	18	52
		%	80,0	81,8	81,3
	Metronidazole+Vancomycin	N	6	2	10
		%	20,0	9,1	15,6
	Not ordinated	N	0	2	2
		%	0,0	9,1	3,1
Total		N	30	22	64
		%	100,0	100,0	100,0

$\chi 2=3,714$; ss=2; p=0,156

A comparison of the average duration of hospital stay by observation groups shows that the longer duration of hospitalization was noted in patients using β lactam antibiotics with an average duration of 20.4±6.7 days (range 8-35 days) and shorter for patients using other antibiotics with an average duration of hospitalization of 19.8±10.3 days (range 1-50 days). According to the median, the comparison of hospital stay, and the observed groups, shows that the longer hospital stay had patients using β lactam antibiotics with a median duration of M=21 days (interquartile range 16-23 days), compared to patients using other antibiotics with a median duration of 17.5 days (interquartile range 13-26 days). The Mann-Whitney analysis shows that there is no significant difference between the observed groups with Z=-0.826, p=0.409; p > 0.05 (Graf 2).



Graph 2. Duration of hospital stay compared by groups

Out of the total number of patients, the fatal outcome was more frequent when β lactam antibiotics were used in 3 or 10% of the cases compared to the group where other antibiotics were used, with a fatal outcome occurred in 1 or 4.5% of the cases. The statistical analysis shows that there is no significant difference from the fatal outcome between groups (p> 0.05) (Table 5).

Table 5. The comparison of categorical variables between groups according to disease outcome

			Outcome		
			Group		Total
			β laktams	Other	
Outcome	Recovered	N	27	21	60
		%	90,0	95,5	93,8
	Died	N	3	1	4
		%	10,0	4,5	6,3
Total		N	30	22	64
		%	100,0	100,0	100,0

$\chi 2$=0,532; ss=1; p=0,466

IV. DISCUSSION

The study involved a total of 64 patients with the presence of *C. difficile*, 41 men and 23 women, aged from 24 to 92. The largest number of registered cases was recorded in 2012, 20 (31.3%), and in 2011, only 2 (3.1%). The median age of patients is 76.5 (67.5-80.8). In a study by Pechal et al., the median age of the respondents was 74 (59–83) years and CDI was the most common in the elderly (> 65 years)[14]. In our study, the relationship between male and female patients was 64.1%: 35.9% in favor of the male sex, in contrast to the study by Stevens et al. where the authors state that the difference in race and sex was not observed [15]. In a study published in 2015 by Natarajan et al., the authors noted that CDI rates in short-term monitoring were 5 times higher in women with non-toxic *C. difficile* strain compared to women without *C. difficile*. The HR (hazard ratio)=5.13 (95% CI:1.47-17.83) and the comparative HR for men was HR=0.44 (95% CI:0.04-4.43). Long-term monitoring, however, produced a similar result for both men and women [16]. Antibiotics are known to be one of the major risk factors for CDI (4), as confirmed in this study, in which 81.2% of patients previously used antibiotics prior to CDI symptoms. Only 18.8% of them did not use antibiotics before the onset of symptoms, including recurrent cases. The most abundant group of used antibiotics was from the β lactam antibiotic group, 46.9%. According to the WHO report on the control of antibiotic consumption in the world from 2016-2018, the most commonly used oral form of antibiotic was amoxicillin, and the most commonly used parenteral antibiotic was ceftriaxone, both from the group of β lactam antibiotics. Other antibiotics account for 34.3%, of which 45.5% were quinolone antibiotics and 18.2% sulphonamides. These findings are not surprising, because the most frequently prescribed antibiotics really are β lactams [17]. Deshpanade et al. in a meta-analytical study [18], investigating the effect of antibiotics on the emergence of community-associated CDI (CA-CDI). The results showed that the greatest risk for developing CA-CDI has clindamycin, fluoroquinolones, and then cephalosporins, where tetracyclines do not increase the risk for CDI [18]. It is also known that the duration of therapy increases the risk of CDI. Since quinolones are the most common in the group of other antibiotics (45.5%), data may suggest that there may be a link between the use of antibiotics, that have an increased risk of developing CDI, and shortening the time of therapy needed to show symptoms of the disease. Although different factors play a role here, above all *C. difficile* strains, comorbidities, immune system function, other treatments in use, age, and the underlying disease that needed the use of antibiotics in the first place.

According to the IDSA/SHEA guideline from 2017, metronidazole is no longer the first choice when it comes to treating CDI. Metronidazole is recommended only for mild/moderate first episodes or when vancomycin or fidaxomicin are not available [12]. According to the results obtained in our study, out of the total number of patients, metronidazole was used in 81.3% of the cases, in combination with vancomycin, in 15.6% of the cases, and vancomycin alone was not used. It is concluded that the therapeutic protocol at the clinic does not match with the IDSA/SHEA guideline from 2017. However, these are relatively new directions, and the data were collected from the period 2011-2019, so it is understandable there is a discrepancy in therapeutic management. The IDSA/SHEA guideline recommendations from 2010 indicate that metronidazole is the first choice for the first mild or moderate CDI episode and the first recurrent episode, and vancomycin for the first severe CDI episode. From this, it is concluded that the therapeutic protocol at the Infectious clinic of the Clinical center of the University of Sarajevo was in correlation with the IDSA/SHEA guideline recommendations from 2010 [19]. Out of the total number of patients, only 3.1% did not require therapeutic treatment because they had an

asymptomatic CDI form. It is interesting that in the group of patients using β lactam antibiotics, there was a need for combined therapy in 20% of the cases, as opposed to the group receiving other antibiotics (9.1%).
By comparing disease outcomes by groups, our study shows that death was more common in the case of using β lactam antibiotics (10%) compared to the group in which other antibiotics were used (4.5%). It is interesting to mention that a recent study from 2020 by Goldstein et al [20] showed that there is a link between the use of penicillin and the increase in mortality caused by sepsis in elderly people in the USA, as well as a link between the use of cephalosporin and the sepsis mortality rate in the age group from 18-49, while no link was found for those over 50 years of age. This study may partially support the result of mortality was higher in the group that used β lactam antibiotics, but it definitely needs to be taken with a reserve because antibiotics are not the only factor that determines the mortality outcome. Many other factors, such as age, comorbidities, drug utilization, main illness, and the state of the immune system have a greater impact on the outcome of the disease.

V. CONCLUSION

Our study showed that pseudomembranous colitis developed in a small percentage of patients who did not use antibiotics at all before the onset of symptoms. Patients undergoing antibiotic therapy had a slightly higher risk of developing *C. difficile* pseudomembranous colitis with β-lactam antibiotics compared with some other antibiotics.

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