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TREATMENT OF PATIENTS AFTER LABORATORY CONFIRMED DIAGNOSIS OF CLOSTRIDIUM DIFFICILE INFECTION

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Abstract. *Compliance with the guidelines for the treatment of Clostridium difficile infection (CDI) is necessary to properly and successfully treat CDI and prevent recurrence of infection. Wrong treatment of CDI patients can lead to suboptimal regimens, such as failure to cure or increased risk of relapse or unnecessary medication and higher hospital costs. The aim of this study was to assess adherence to the CDI treatment algorithm from the moment of diagnosis: this was defined as therapy consisting of the appropriate antibiotic, route, dose and duration based on the severity of infection and episode. A retrospective cohort study of CDI cases diagnosed on admission or during hospitalization was conducted. In the treatment of our patients diagnosed with post-antimicrobial diarrhea caused by C. difficile, metronidazole and vancomycin were most often prescribed. The results showed that there was a difference ($p < 0.001$) in the way CDI patients were treated based on the severity of clinical presentation, so that 54.3% of patients was not treated according to the guidelines. The greatest irregularity was observed in patients with severe clinical presentation (85.7%) and with complications (82.6%). The treatment non-adherence was mainly shown in patients with a mild and/or moderate clinical presentation (63.9%). A statistically significant difference was observed in the treatment method of CDI in patients with primary infection and with repeated infection ($p = 0.006$). In most forms of manifestation of CDI, metronidazole was prescribed in over 50% of the wrong therapy. The adherence of choosing the treatment and respect the currently valid guidelines for the treatment of patients with CDI infections must be applied based on the severity of the clinical presentation. Continuing education of healthcare workers on the diagnosis and treatment of CDI can be beneficial, especially if the guidelines are revised.*

Key words*: Clostridium difficile infection, antibiotics, probiotics, algorithm, guidelines*

Introduction

Infections of the colon caused by the bacterium *C. difficile* occur in patients with disrupted normal gut flora, typically due to recent antibiotic use [1]. The most common clinical manifestation of *C. difficile* infection (CDI) is *C. difficile* colitis. Symptoms and signs of a moderate clinical presentation include frequent watery stools with an unpleasant odor, greenish color, with or without pathological admixtures (mucous, bloody, or mucopurulent), elevated body temperature, fever, abdominal pain, and cramps in the lower quadrants. In severe cases, life-threatening

signs and symptoms appear, such as nausea and vomiting, weakness, loss of appetite, pronounced dehydration, bloating, peripheral edema, and hypovolemic shock [2,3]. The most severe form of the disease is fulminant colitis. The significant increase in the incidence of fulminant colitis in recent years has been associated with highly virulent strains of *C. difficile*, such as NAP1/027/BI [4]. The mortality rate from CDI is estimated at 5%, with complications increasing to 15-25%, and up to 34% in intensive care units. Comorbidities such as ischemic diseases of the liver, kidneys, and heart contribute to higher mortality rates, especially in older patients (>70 years) [5]. The treatment of patients with CDI is based on patient characteristics and the severity of the clinical presentation. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published the first guidelines for CDI treatment in 2009, which were updated in 2014 [6]. There is a growing data in literatures on antimicrobial treatment of CDI and newer therapeutic approaches, such as fecal microbiota transplantation (FMT) and monoclonal antibody toxin binding, leading ESCMID to update and publish new guidelines in 2021 [7,8]. The first step in treatment is the discontinuation of the antibiotic that caused the infection, as prolonged antibiotic therapy can affect the risk of CDI recurrence. Empirical antibiotic therapy for CDI should only be initiated when there is expected significant delay in laboratory confirmation of the diagnosis or in cases of fulminant CDI. Vancomycin or fidaxomicin are the drugs of choice for treating the first episode of CDI. Oral vancomycin is recommended at a dose of 125 mg four times daily, or 200 mg fidaxomicin twice daily. The therapy should last for 10 days. If vancomycin or fidaxomicin are unavailable and the patient has a milder form of infection, metronidazole 500 mg three times daily orally for 10 days can be used. Long-term use of metronidazole is not recommended due to neurotoxicity. Oral vancomycin is the therapy of choice for fulminant CDI at a dose of 500 mg four times daily [9]. For the first recurrence of CDI, prolonged oral therapy with vancomycin with pulsed or tapered doses is recommended: 125 mg four times daily for 10-14 days, then reduced to twice daily for one week, then once daily for one week, and finally once every two or three days for 2-8 weeks. The first recurrence of CDI can also be treated with fidaxomicin for 10 days instead of the standard 10-day vancomycin regimen if vancomycin was used initially. If metronidazole was used as initial therapy for the first episode of CDI, then vancomycin should be used for the first recurrence in the standard 10-day regimen. For treating multiple recurrences of CDI, prolonged vancomycin therapy with pulsed or tapered doses is recommended [9]. FMT is one of the important newer approaches to CDI treatment. FMT involves the infusion of a suspension of healthy donor feces into the patient's colon. FMT restores the gut flora of the affected person by transferring bacteria from the healthy donor's gut flora [10,11]. There are three primary reasons for FMT in CDI patients: (1) multiple recurrent CDI, (2) moderate CDI unresponsive to standard therapy (vancomycin or fidaxomicin) for at least one week, and (3) severe or fulminant CDI unresponsive to standard therapy for 48 hours [12].

The aim of this study was to assess adherence to the CDI treatment algorithm from the time of diagnosis: appropriate antibiotic, method of administration, dose, and duration based on the severity of infection and episode.

Methods

A retrospective cohort study on CDI cases, diagnosed either upon admission or during hospitalization, and the method of antibiotic therapy administration, encompassed 116 patients at the University Clinical Center of the Republic of Srpska from July 2019 to December 2020. Data on the administered antibiotic therapy, type of antibiotics, method of administration, timing of the first dose, need for redosing, duration of antibiotic use, prophylactic use of antibiotics, were obtained from electronic medical records. The use of antimicrobial drugs according to the severity of the clinical presentation of CDI was categorized into mild/moderate, severe, and severe with complications. Recurrent CDI cases were defined as those with recurrent diarrhea after completing therapy, confirmed by a positive laboratory test, occurring more than two weeks but less than eight weeks after the onset of the previous episode (regardless of the location of the episode). The term "recurrent case" was used to also denote relapses caused by the same strain of *C. difficile* and reinfection with a different strain of the bacterium. CDI cases with symptoms appearing more than eight weeks after the onset of the previous episode were considered new CDI cases [13]. Patients with negative laboratory test results for *C. difficile* as well as those who were not tested were excluded from the study.

Data were analyzed using descriptive and analytical statistical methods. The statistical software package SPSS, version 25.0, was used for data processing, with a 95% confidence interval for statistical significance.

Results

The results showed a statistically significant difference in the frequency of metronidazole and vancomycin use before and after CDI diagnosis. Metronidazole ($p < 0.001$) and vancomycin ($p < 0.001$) were significantly more frequently used after the CDI diagnosis compared to the period before the diagnosis. Post-diagnosis, metronidazole was used in 76.7% and vancomycin in 39.7% of patients, whereas pre-diagnosis, metronidazole was used in 8.6% and vancomycin in 2.6% of CDI patients (Table 1).

Table 1. Antibiotics before and after the diagnosis of CDI.

Before diagnosis	After diagnosis						p-value (MN)
	Yes		No		Total		
	n	%	n	%	n	%	
Metronidazole							
Yes	4	40.0	6	60.0	10	8.6	<0.001
No	85	80.2	21	19.8	106	91.4	
Total	89	76.7	27	23.3	116	100.0	
Vancomycin							
Yes	1	33.3	2	66.7	3	2.6	<0.001
No	45	39.8	68	60.2	113	97.4	
Total	46	39.7	70	60.3	116	100.0	

CDI, *Clostridioides difficile* infection; MN, McNemar test

Table 2 shows that prior to diagnosis, the oral administration of metronidazole was significantly lower (6.9%), whereas after diagnosis, it increased significantly (64.7%). Parenteral administration of metronidazole also increased post-diagnosis (12.9%) compared to pre-diagnosis (1.7%). Vancomycin was administered orally in 1.7% and parenterally in 0.9% of patients before diagnosis; post-diagnosis, it was administered orally in 16.4% and parenterally in 23.3% of patients ($p < 0.001$) (Table 2).

Table 2. Type and method of administration antibiotics.

Before diagnosis	After diagnosis								p-value (MN)
	PO		IV		No Vancomycin		Total		
	n	%	n	%	n	%	n	%	
Metronidazole									
PO	4	50.0	0	0.0	4	50.0	8	6.9	<0.001
IV	0	0.0	1	50.0	1	50.0	2	1.7	
No Metronidazole	71	67.0	14	13.2	21	80.8	106	91.4	
Total	75	64.7	15	12.9	26	22.4	116	100.0	
Vancomycin									
PO	0	0.0	0	0.0	2	100.0	2	1.7	<0.001
IV	0	0.0	1	3.7	0	0.0	1	0.9	
No Vancomycin	19	16.8	26	23.0	68	60.2	113	97.4	

Total	19	16.4	27	23.3	70	60.3	116	100.0

CDI, *Clostridium difficile* infection; PO, Per os; IV, Intravenous; MN, McNemar test

There was a highly significant difference ($p < 0.001$) in the treatment methods of CDI patients based on the severity of the clinical presentation, with 54.3% of patients not treated according to guidelines. The greatest discrepancies were observed in patients with severe clinical manifestations (85.7%) and severe manifestations with complications (82.6%). Proper treatment choice was mainly observed in patients with mild and/or moderate clinical presentations (63.9%) (Table 3).

Table 3. Treatment appropriateness by severity CDI.

Severity	**Antibiotic treatment**						**p-value**
	Appropriate		**Inappropriate**		**Total**		
	n	%	n	%	n	%	(χ^2)
Mild to moderate	46	63.9	26	36.1	72	62.1	<0.001
Severe	3	14.3	18	85.7	21	18.1	
Severe and complicated	4	17.4	19	82.6	23	19.8	
Total	53	45.7	63	54.3	116	100.0	

CDI, *Clostridium difficile* infection; χ^2, Chi-squared test

Table 4 shows a statistically significant difference in CDI treatment methods between patients with primary and recurrent infections ($p = 0.006$). Recurrent infections were treated incorrectly in 80.8% of cases regarding antibiotic choice and administration method (Table 4).

Table 4. Antibiotic treatment and type CDI.

Type of CDI	**Antibiotic treatment**						**p-value**
	Appropriate		**Inappropriate**		**Total**		
	n	%	n	%	n	%	(χ^2)
Initial CDI	47	52.8	42	47.2	26	22.4	0.06
Recurrence CDI	5	19.2	21	80.8	89	76.7	
Unknown	1	100.0	0	0.00	1	0.9	
Total	53	45.7	63	54.3	116	100.0	

CDI, *Clostridium difficile* infection; χ^2, Chi-squared test

In most clinical manifestations of CDI, over 50% of incorrect therapies involved prescribing metronidazole. In mild and/or moderate clinical cases, metronidazole was used incorrectly due to recurrent CDI, while in severe and complicated cases, it was used improperly due to the incorrect route of administration

(oral). Vancomycin was mis administered (IV) in all clinical forms of CDI: 30.7% in mild/moderate, 28.6% in severe with complications, and 22.2% in severe cases. It was noted that a combination of both drugs was administered in all forms of CDI, predominantly in severe clinical cases (27.8%) (Figure 1).

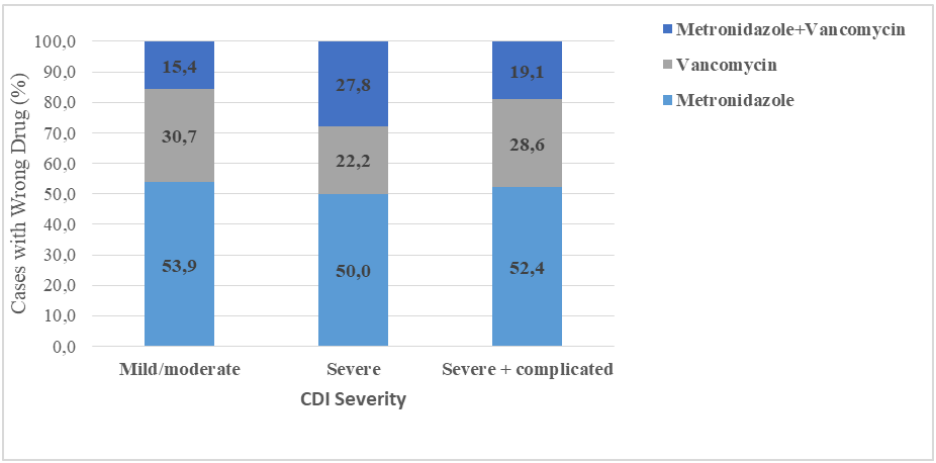

Figure 1. Components of wrong drug by severity.

Discusion

In the treatment of our patients diagnosed with post-antimicrobial diarrhea caused by *C. difficile*, metronidazole and vancomycin were the most prescribed medications. Initially, before the laboratory-confirmed diagnosis of CDI, a smaller number of patients were on therapy. It was observed that before CDI diagnosis, primary CDI was treated with oral metronidazole significantly more frequently ($p = 0.005$) (14.8%) compared to recurrent CDI (4.5%). Similar results were obtained for the treatment of primary and recurrent infections with vancomycin ($p = 0.006$). In most included cases, both C. difficile positive and negative post-antibiotic diarrhea, the study by Maslennikov et al. (2022) utilized a combination of oral antibiotics (metronidazole and/or vancomycin) and the probiotic S. boulardii for treatment. In fewer cases, these drugs were applied separately. Relapse of C. difficile following successful treatment with oral vancomycin was recorded in only one patient. This relapse was successfully treated with a combination of oral vancomycin and metronidazole [14]. In the study by Marinescu et al. (2021), vancomycin (35%), metronidazole (12.5%), and vancomycin/metronidazole (10%) were used for treating CDI patients, with combinations of metronidazole/rifaximin (10%) and vancomycin/rifaximin (32%) also being employed in definite cases [15]. The study by Filippidis et al. (2022) showed that metronidazole was more frequently administered (83.7%) compared to patients treated with vancomycin (12.1%) and those treated with fidaxomicin (4.1%). A composite outcome, which included mortality, clinical failure, or recurrence, was observed in 39.8% of CDI patients. The use of metronidazole or vancomycin was associated with the composite outcome alongside the Charlson comorbidity index score and leukocyte count > 15 g/L [16].

Tay et al. (2019) also found that oral metronidazole, used for severe CDI, was associated with persistent diarrhea, complications, and mortality. Most CDI patients used oral metronidazole as the sole treatment (92.6% for mild to moderate CDI, 83.9% for severe, 77% for severe complicated) [17]. According to our results, there was a highly significant difference ($p < 0.001$) in the treatment methods of CDI patients based on the severity of the clinical presentation, with 54.3% of patients not treated according to guidelines. The greatest discrepancy was observed in patients with severe clinical manifestations (85.7%) and severe manifestations with complications (82.6%). Proper treatment selection was mainly observed in patients with mild and/or moderate clinical presentations (63.9%). A statistically significant difference was also noted in the treatment of CDI between patients with primary and recurrent infections ($p = 0.006$). Recurrent infections were treated incorrectly in 80.8% of cases regarding the choice of antibiotics and the method of drug administration. For most forms of CDI clinical presentation, over 50% of incorrect therapies involved prescribing metronidazole. In mild and/or moderate clinical cases, metronidazole was used incorrectly due to recurrent CDI, and in severe and complicated cases, it was used improperly due to the incorrect route of administration (oral). Vancomycin was mis administered (IV) in all clinical forms of CDI: 30.7% in mild/moderate, 28.6% in severe with complications, and 22.22% in severe cases. It was noted that a combination of both drugs was administered in all forms of CDI, predominantly in severe clinical cases (27.8%). Adherence to guidelines for the treatment of CDI is essential for correctly and successfully treating CDI and preventing the recurrence of the infection. The study by Aljafel et al. (2020) showed that adherence to relevant global guidelines for CDI treatment was significantly associated with clinical cure [18]. Incorrect treatment of CDI patients can lead to suboptimal regimens, such as non-cure or increased risk of recurrence, unnecessary medication use, increased risk of side effects, and higher hospital costs. The study by Elbeddini and Gerochi (2021) on compliance with CDI treatment guidelines indicated that patients with severe CDI were the most treated contrary to the guidelines (83%), with the primary factor contributing to severe CDI being the prescription of the wrong antibiotic (72%). Patients who received inappropriate therapy also had a higher 30-day mortality rate. Mild to moderate CDI cases were mostly treated with vancomycin monotherapy or a combination of metronidazole/vancomycin. For severe CDI, more than half of the cases were treated with metronidazole monotherapy (55%), while incorrectly treated CDI patients were prescribed combination therapy [19].

Conclusion

The proper selection of treatment and adherence to the current guidelines for treating patients with CDI infections should be based on the severity of the clinical presentation. Continuous education of healthcare professionals on the diagnosis and treatment of CDI can be beneficial, especially if the guidelines are adapted accordingly.

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LIJEČENJE PACIJENATA NAKON LABORATORIJSKI POTVRĐENE DIJAGNOZE CLOSTRIDIUM DIFFICILE INFEKCIJE

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Sažetak. *Usklađivanje sa smjernicama za liječenje Clostridium difficile infekcije (CDI) je neophodno kako bi se pravilno i uspješno liječila CDI i spriječilo ponovno pojavljivanje infekcije. Pogrešno liječenje CDI pacijenata može da dovede do suboptimalnih režimima, kao što su neizliječenje ili povećani rizik od recidiva ili nepotrebnog uzimanja lijekova i većih bolničkih troškova. Cilj ovog istraživanja je bio da se procijeni pridržavanje algoritma liječenja CDI od momenta postavljanja dijagnoze: odgovarajući antibiotik, način primjene, doza i trajanje na osnovu ozbiljnosti infekcije i epizode. Sprovedeno je retrospektivno kohortno istraživanje CDI slučajeva kojima je dijagnoza postavljena na prijemu ili tokom hospitalizacije. U terapiji naših pacijenata sa dijagnozom postantimikrobne dijareje uzrokovane sa C. difficile najčešće su propisivani metronidazol i vankomicin. Rezultati su pokazali da je postojala značajna razlika ($p < 0,001$) u načinu liječenja pacijenata sa CDI na osnovu težine kliničke slike, tako da 54,3% pacijenta nije liječeno u skladu sa smjernicama. Najveća nepravilnost je uočena kod pacijenata sa teškom kliničkom slikom (85,7%) i sa teškom kliničkom slikom sa komplikacijama (82,6%). Pravilan način izbora liječenja se uglavnom pokazao kod pacijenata sa blagom i/ili umjerenom kliničkom slikom (63,9%). Uočena je statistički značajna razlika i u načinu liječenja CDI kod pacijenata sa primarnom infekcijom i sa ponovljenom infekcijom ($p = 0,006$). Kod većine oblika ispoljavanja kliničke slike CDI, od pogrešne terapije u preko 50% slučajeva je propisivan metronidazol. Pravilan način izbora liječenja i poštovanje trenutno važećih smjernica za liječenje pacijenata sa CDI infekcijama treba da se primjenjuje na osnovu težine kliničke slike. Kontinuirana edukacija zdravstvenih radnika o dijagnostici i liječenju CDI može da bude od koristi naročito ako su prilagođavane smjernice.*

Ključne riječi*: Clostridium difficile infekcija, antibiotici, probiotici, algoritam, smjernice*