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ECONOMIC ASPECTS OF TREATMENT AND MANAGEMENT OF CLOSTRIDIOIDES DIFFICILE INFECTIONS IN UNIVERSITY CLINICAL HOSPITAL MOSTAR

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SUMMARY

Treatment of Clostridioides difficile infections in University Clinical Hospital Mostar from an economic perspective Clostridioides difficile is the most prominent pathogen directly tied to a healthcare system and proven to be one of the main causes of high economic impacts. It results in a frequent need for hospitalization, including the treatment of sepsis and post-acute care, and requires an extended number of days spent at the hospital. In addition to the costs of the medicine and laboratory analysis, extended hospitalization is the key component of the high healthcare expenses. The rational use of antibiotics, mandatory implementation of general hygiene measures, like washing hands, and disinfecting surfaces can significantly contribute towards hospital's overall expenses. This is particularly important for those in contact with an infected patient or with a patient suspected of having CDI. These basic measures establish security systems in the prevention of CDI. Proper managing and forecasting of the costs on the annual level for each individual healthcare institution is a necessary measure. Developing an accurate estimate of the funds needed for the treatment and prevention of CDI and its best therapies for each form of the disease, is a secure way to prevent recurring episodes that cause a significant economic burden on healthcare institutions.

Key words: *Clostridioides difficile, infection, treatment, healthcare expenses, hospital treatmet*

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INTRODUCTION

The first important document on the treatment and management of Clostridioides difficile, previously known as Clostridium difficile infection (CDI), was published by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) in 2009. The same document was updated in 2014. The latest guideline update from 2021 established that the definition of CDI treatment remains unchanged, while the definition of treatment response for severe CDI is modified (1). The Infectious Diseases Society of America (IDSA) together with the Society for Healthcare Epidemiology of America (SHEA) significantly changed their recommendations for treating initial CDI episodes in 2017, as well as the overall approach to healthcare due to the high costs of treating with newer drugs, which they determined have lower disease recurrence rates when applied (2). Demographic aging of the population along with widespread use of antibiotics, especially in hospital settings, has led to a high frequency of CDI in both developed and developing countries and is considered the leading cause of hospital-acquired infections globally. Antibiotic use can be accompanied by numerous adverse effects, most commonly occurring in the gastrointestinal system (3). Depending on the type of antibiotic, epidemiological circumstances, and the population from which the patient originates, diarrhea occurs in 25 to 50% of patients receiving antibiotic treatment. Although a decrease in CDI incidence has been observed in recent years, the occurrence of more severe clinical forms of the disease is still present (2). Factors that lead to significant increases in morbidity, mortality, prolonged hospital stays, frequent readmissions, increased treatment costs result in additional burden on healthcare systems of each individual country (4). Proper antibiotic selection during the first episode of illness is crucial for reducing the main risk factor, which are recurrent and recurring episodes, based on which treatment strategy is determined for each individual patient (5).

Clostridioides difficile is a ubiquitous spore-forming bacterium that can be found in water, soil, the digestive system of numerous domestic animals, and in the digestive system of healthy children and adults. O'Tolle and Hall discovered the bacterium Clostridioides difficile in newborn feces in 1935 and named it Bacillus difficilis due to its extremely complicated and difficult cultivation (7). With the discovery of antibiotics and their increasingly frequent use during the 20th century, there was an increase in the incidence of diarrhea caused by C. difficile, which occurs particularly often after clindamycin use. Clindamycin-associated colitis began to

be more intensively studied in the 1970s when the extreme importance of C. difficile toxins in disease pathogenesis was proven (8). From that period until today, due to the increase in incidence of severe forms of the disease and the increasingly frequent occurrence of recurrent disease, the medical and economic significance of C. difficile infection has grown and has been characterized as an "urgent threat" to public health according to data from the Centers for Disease Control and Prevention (9). The aim of this study is to examine the impact of new approaches to CDI treatment on economic expenditures of treatment and treatment outcomes of patients at the Clinic for Infectious Diseases of the University Clinical Hospital Mostar compared to treatment with therapy not recommended by the latest guidelines in the time period from January 1, 2018, to May 31, 2023, covering the period before the SARS-COV-2 pandemic, during the SARS-COV-2 pandemic, as well as the period after the SARS-COV-2 virus pandemic.

SUBJECTS AND METHODS

The purpose of this study is to determine how much the treatment and management as well as the provision of healthcare for mild CDI, moderately severe CDI, severe CDI, and recurrent CDI economically burden the hospital institution and to define healthcare when treating CDI. The purpose of the study can also be characterized as applicative due to possible practical value because the obtained data can determine the costs that go toward treating this infection as a complication of hospital treatment and predict the funds that need to be secured annually for infection treatment so that economic expenditures can be controlled in a planned manner, which is important for every healthcare institution.The conducted study included all patients with confirmed CDI diagnosis who were treated at the Clinic for Infectious Diseases of the University Clinical Hospital in Mostar from January 1, 2018, to May 31, 2023. Demographic data (age, gender) and epidemiological data were analyzed - first episode of illness, recurrent episodes of illness (rCDI), number of days of hospital stay, type of admission to the Clinic (admission from home conditions, transfer from other clinics, departments, hospitals), admissions from residential institutions, previous hospital stay within the past four months, applied antibiotic therapy, total monetary amount of treatment. A variable that was also analyzed was whether the patient had SARS-COV-2 infection due to the time period of the conducted study since the pandemic was declared during the time period covered by the conducted study. The study is retrospective cohort by its characteristics. Data for 208 patients were used in the conducted study. The study itself was divided into collecting data about the studied group obtained from medical documentation, hospital information system and data from the Billing Unit of University Clinical Hospital Mostar and the Information Technology Service of University Clinical Hospital Mostar, entering the obtained data into the computer, statistical data processing, tabular presentation and interpretation of the obtained data.

Statistical analysis of data was performed using IBM SPSS Statistics for Windows, version 25 (Armonk, NY: IBM Corp.). Categorical variables were expressed as number and percentage, and numerical variables as median and first and third quartiles. Normality of distribution of numerical variables was tested using the Kolmogorov-Smirnov test. Differences in prevalence were tested using the Chi-square test, and for testing differences in numerical variables, the Mann-Whitney U test and Kruskal Wallis H test were used. The statistical significance threshold was set at alpha=0.05. P values that could not be expressed to three decimal places were expressed as $p<0.001$.

RESULTS

In the period from January 1, 2018, to May 31, 2023, at the Clinic for Infectious Diseases of the UniversityClinical Hospital Mostar, a total of 208 patients were treated for infections caused by the bacterium Clostridioides diffiile (Table 1). The oldest patient was 93 years old, and the youngest was 17 years old. The mean age of patients was 74.5, and half of the patients were between 66 and 81 years old. The mean length of stay in the department was 9.0 days, with half of the patients staying between 6 and 12 days. Among CDI patients, those with the first episode significantly predominated ($\chi2=7.692$; $p=0.006$) (Table 2). Analysis of the number of CDI patients by year showed significantly higher representation of these patients in the period 2020–2022 than in other years from the observed period ($\chi2=89.000$; $p<0.001$) (Table 3). No significant difference was found in the distribution of CDI patients by gender ($\chi2=1.558$; $p=0.212$) (Table 3). Most CDI patients had more than one diagnosis ($\chi2=38.942$; $p<0.001$) (Table 4). In 151 patients, the primary diagnosis was enteritis caused by Clostridium difficile (code A04.7). Most patients were hospitalized within 4 months of admission to another department ($\chi2=108.173$; $p<0.001$) (Table 5). Most CDI patients had recovered from coronavirus disease (were SARS-COV-2 positive) ($\chi2=10.173$; $p=0.001$) (Table 6). A statistically significant difference was found in the distribution of patients by disease severity ($\chi2=40.856$; $p<0.001$). Half of the patients had moderately severe disease caused by Clostridium difficile (Table 7). A statistically significant difference was found in the distribution of patients by therapy ($\chi2=62.923$; $p<0.001$). Most patients were treated with a combination of metronidazole and vancomycin (Table 8). Most patients felt improvement after therapy ($\chi2=239.433$; $p<0.001$) (Table 9). Deterioration was found in two patients with severe disease (Table 9). No statistically

significant difference was found in treatment outcome by therapy ($\chi2$=4.616; p=0.289; Fisher's exact test) (Table 10).

Table 1. Distribution of CDI patients by year

Year	n	%
2018	16	7,7
2019	18	8,7
2020	36	17,3
2021	72	34,6
2022	56	26,9
2023	10	4,8
total	208	100,0

Table 2. Distribution of patients by disease episode

Episode	n	%
First	124	59,6
Recurrent	84	40,4
Total	208	100,0

Table 3. Distribution of patients by gender

Gender	n	%
Male	95	45,7
Female	113	54,3
Total	208	100,0

Table 4. Distribution of patients by number of diagnose

Number of diagnoses	n	%
One	59	28,4
Multiple	149	71,6
Total	208	100,0

Table 5. Distribution of patients by hospitalization within 4 months

Hospitalized within 4 months	n	%
No	29	13,9
Yes	179	86,1
Total	208	100,0

Table 6. Distribution of patients by recovered SARS COV 19 disease

Had SARS COV 19	n	%
no	81	38,9
yes	127	61,1
Total	208	100,0

Table 7. Distribution of patients by disease severity

Disease severity	n	%
Mild	73	35,1
Moderate	105	50,5
Severe	30	14,4
Total	208	100,0

Table 8. Distribution of patients by therapy

Therapy	n	%
Metronidazol	60	28,8
Combination	120	57,7
Vankomicin	28	13,5
Total	208	100,0

Table 9. Distribution of patients by outcome

Clinical outcome	n	%
Mortality	33	15,9
Clinical improvement	173	83,2
Clinical deterioration	2	1,0
Total	208	100,0

Table 10. Treatment outcome by type of therapy

	Metronidazol		Kombinirano		Vankomicin	
Outcome	n	%	n	%	n	%
Mortality	11	18,3	19	15,8	3	10,7
Clinical improvement	47	78,3	101	84,2	25	89,3
Clinical improvement	2	3,3	0	0,0	0	0,0
Total	60	100,0	120	100,0	28	100,0

No statistically significant difference was found in the distribution of patients who continued therapy after initial treatment ($\chi2$=0.347; p=0.841) (Table 11).

Table 11. Continuation of treatment by type of therapy

	Metronidazol		Combined		Vankomicin	
Extended therapy	n	%	n	%	n	%
No	15	25,0	28	23,3	8	28,6
Yes	45	75,0	92	76,7	20	71,4
Total	60	100,0	120	100,0	28	100,0

Total treatment costs and therapy costs by year are shown in Table 12. Total hospital treatment costs and therapy costs by type of therapy are shown in Table 13

Table 12. Total treatment costs and therapy costs by year

Year	Treatment costs (BAM)	Therapy costs (BAM)
2018	36422,81	1475,60
2019	43934,52	1611,05
2020	87193,05	13855,05
2021	277624,64	39373,05
2022	198187,63	42360,90
2023	33808,61	7873,05
Total	677171,26	106548,70

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Table 13. Treatment and therapy costs by type of therapy

	Total	C [Q1-Q3]*
Treatment costs (BAM)		
Metronidazol	169915,91	1645,51 [1127,03; 3012,09]
Combined	428054,98	2774,37 [1895,60; 4335,80]
Vankomicin	79200,37	2203,40 [1430,90; 3597,51]
Therapy costs (BAM)		
Metronidazol	3357,40	27,30 [22,43; 39,00]
Combined	83037,60	597,45 [348,28; 991,78]
Vankomicin	20153,70	646,83 [448,00; 925,65]

*C [Q1-Q3] – Median [first quartile; third quartile]

A statistically significant difference was found in hospital treatment costs by type of therapy (Kruskal-Wallis H=14.579; p=0.001). Hospital treatment costs for patients treated with metronidazole alone were significantly lower than hospital treatment costs for patients treated with combination therapy (Mann-Whitney U=181.500; p<0.001). Hospital treatment costs by therapy are shown in Figure 1.

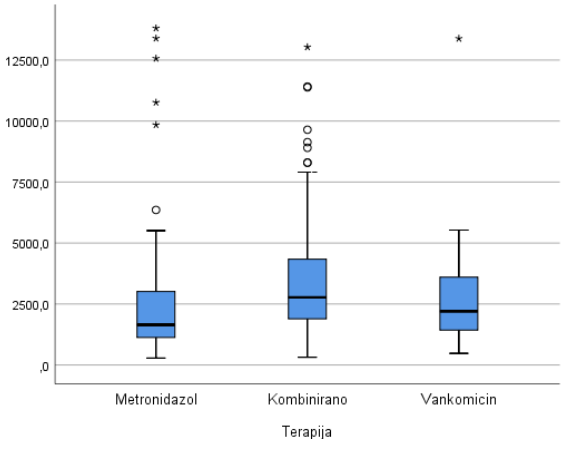

Figure 1. Hospital treatment costs by therapy

A statistically significant difference was found in therapy costs by type of therapy (Kruskal-Wallis H=115.440; p<0.001). Therapy costs for patients treated with metronidazole alone were significantly lower than therapy costs for patients treated with combination therapy (Mann-Whitney U=181.500; p<0.001) as well as therapy costs for patients treated with vancomycin (Mann-Whitney U=37.000; p<0.001). Therapy costs by therapy are shown in Figure 2.

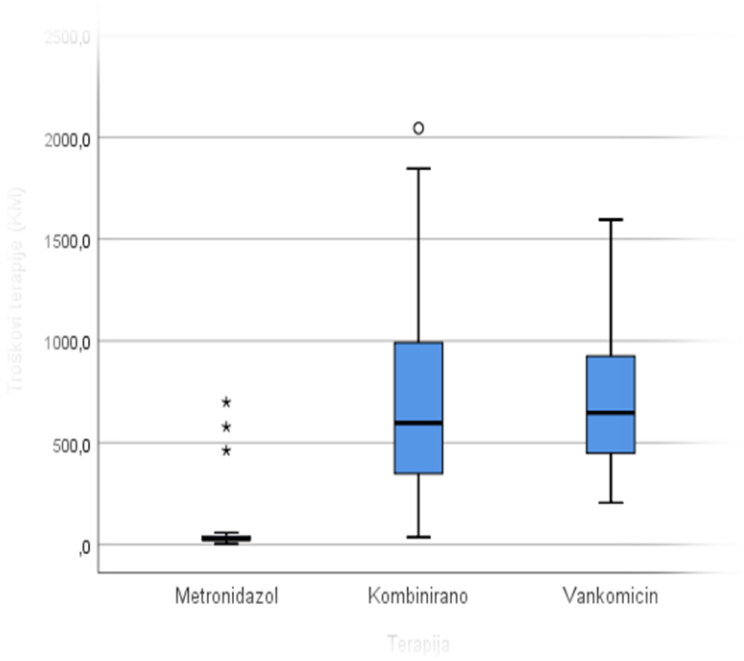

Figure 2. Therapy costs by therapy

Analysis of the share of therapy costs in treatment costs shows a mean value of 14.45%, with therapy costs representing between 3.15% and 26.48% of total treatment costs for half of the patients.

DISCUSSION

In our study, the number of CDI patients we monitored by year showed significantly higher representation in the period 2020–2022 than in other years of the observed period. During 2020, 17.3% of the total number were treated, in 2021, 34.6% were treated, and during 2022, 26.9%. Since the above-mentioned period coincides with the SARS-COV-2 virus pandemic period, we can conclude that during pandemic years, the number of CDI infections at the Clinic for Infectious Diseases of the University Clinical Hospital Mostar was on the rise. According to Kelly R Reveles and colleagues, hospitals during the pandemic suffered high numbers and flow of patients in general and intensive care departments, and inadequate staff as well as lack of personal protective equipment and prioritizing COVID-19 over traditional healthcare-associated infections, especially early in the pandemic and during waves, increased hospital antibiotic prescribing (2). In a systematic review and meta-analysis by Langford and colleagues, 62.4% of all COVID-19 patients received at least 1 antibiotic. Among them, the most commonly prescribed antibiotics were fluoroquinolones (20.0%), macrolides (18.9%), β-lactam/β-lactamase inhibitors (15.0%), and cephalosporins (15.0%), with 8.6% of COVID-19 patients having concomitant bacterial infection, suggesting that many of these prescribed antibiotics may not have been necessary (24). Of the total 208 patients, 59.6% had their first episode of illness, while the remaining 40.4% developed recurrent episodes of illness. Most CDI patients had more than one diagnosis. In 151 patients, the primary diagnosis was enteritis caused by Clostridioides difficile bacterium (A04.7). The majority of patients, 86.1%, were hospitalized within 4 months in the hospital system. According to Jessica A. Bowman et al., a strong risk factor is hospitalization and contact with healthcare personnel, which is why the burden of this infection mainly affects older patients with comorbidities who have been treated with antibiotic therapy in the recent past (13).

Khanna et al. in their studies conducted in the USA showed that patient movement between healthcare institutions directly affects CDI occurrence. They used a network approach and showed that increased transmission in University hospitals was 4.5% (21). By analyzing disease severity, we found that there is a significant statistical difference in patient representation. Half of the patients had moderately severe disease 50.5%, mild disease was present in 35.1% of patients, while severe disease developed in 14.4% of patients. In CDI treatment, antibiotic therapy with metronidazole, vancomycin, or a combination of these two antibiotics was applied depending on the patient's clinical condition,

first or repeated episode of illness, where we reached the following results: 28.8% of patients were treated with metronidazole. Of the total patients treated with metronidazole, 78.3% improved, 18.3% died, and deterioration was recorded in 3.3% of patients. Patients treated with a combination of intravenous metronidazole and oral vancomycin represent 57.7% of the total number treated, where improvement was recorded in 84%, deaths were 15.8%, and there were no deteriorated patients on combination therapy. Oral vancomycin therapy was received by 13.5% of the total number of treated patients, of which improvement was recorded in 89.3%, there were no deteriorated patients, while those with fatal outcome were 10.7%, which indicates that the lowest mortality rate occurs when patients are treated with vancomycin capsules according to prescribed doses and sufficient treatment duration. After discharge from the hospital system, follow-up of patients who continued therapy according to the scheme was continued, where it was noticed that the proportion of patients treated with metronidazole in hospital conditions required continuation of therapy in 75.0%. In patients treated with a combination of both antibiotics, continuation of treatment after improvement and discharge from the hospital system was recorded in 76.7% of patients. The best and fastest recovery during hospital treatment was shown in situations when patients were treated with oral vancomycin capsules.

It is important to note that during the observed period, we were repeatedly faced with a shortage of vancomycin capsules, and patients were treated with substitutes suggested by guidelines (vancomycin solution powder orally, vancomycin enemas rectally), whose effectiveness is difficult to measure due to the drug's passage through the upper digestive system, direct effect of gastric acid on the orally taken drug preparation, and passage of the drug through the duodenum and jejunum. A limitation in the research was also a certain number of patients whose health condition did not allow the use of oral vancomycin capsules due to lack of swallowing ability. Despite the mentioned limitations, the fastest recovery was recorded in patients on vancomycin monotherapy (capsules, suspension, enema) during hospitalization, with extended vancomycin treatment scheme applied in 71.5% of patients. In statistical data processing, no statistically significant difference was proven between the use of metronidazole, combination of metronidazole and vancomycin, and vancomycin monotherapy after hospital discharge, but we believe that the above-mentioned limitations significantly influenced the research results. A statistically significant difference was found in therapy costs by type of therapy. Metronidazole therapy costs are significantly lower than combination therapy costs and vancomycin costs. Low metronidazole treatment costs are justified by the fact that metronidazole itself is significantly cheaper to procure compared to vancomycin. Metronidazole was the preferred choice in 28.8%. According to ESCMID guidelines, it is still the choice in the absence of vancomycin and fidaxomicin, but for milder forms of disease and in our conditions is still effective due to good sensitivity of Clostridium difficile toxin B (TcdB) to the drug.

In the observed period, we noticed that combination therapy of both drugs represents the greatest economic burden for the institution. With this observation, we must emphasize that treated patients very often had other comorbidities - as many as 71.6% had more than one medical diagnosis, average age of 74.5 years, patients spent from at least 6 days to a maximum of 12 days in the hospital system, on average staying 9 days in the hospital. According to H.E. Burton et al., about 25% of patients treated with vancomycin and metronidazole develop disease recurrence. From 40 to 60% of patients after the first recurrence develop subsequent episodes, which represents the biggest obstacle to recovery, and enormous resources are spent in this vicious cycle of infection-reinfection, increasing morbidity, mortality, reducing quality of life and work capacity (20). In the observed period at the Clinic for Infectious Diseases UKB Mostar, there were 40.4% recurrent infections, which suggests that in the future we need to consider the use of fidaxomicin because previous research has shown that fidaxomicin has minimal effects on intestinal flora and pronounced preventive effect on sporulation and regrowth of C. difficile spores compared to vancomycin and metronidazole (20). Analyzing data for the observed period, funds spent on treatment amount to 106,548.70 BAM, and the amount spent on overall treatment is 677,171.26 BAM, which tells us that the economic burden of CDI treatment is significant, serious, and included treatment of sepsis, provision of post-acute care, prolonged treatment, and complications of prolonged bed rest. We analyzed therapy costs in relation to overall treatment costs where we recorded a mean value of 14.45%, with therapy costs representing between 3.15% and 26.48% of total treatment costs for half of the patients.

CONCLUSION

1. In our study, a statistically significant difference in treatment costs by type of therapy was proven.
2. The best and fastest recovery of patients during hospital treatment in our institution was shown in cases when patients were treated with oral vancomycin capsules.
3. Vancomycin capsule monotherapy proved significantly more cost-effective from an economic perspective than combination therapy of vancomycin and metronidazole for both first and recurrent episodes of illness.
4. Funds should be allocated not only for medications but also for comprehensive patient care, considering the extended number of days of stay in the

institution and frequent recurrent episodes of illness. A certain portion of economic resources should be allocated and directed toward education of healthcare and non-healthcare staff, working on improving control and supervision of hospital infections.

5. Services in the system that assess necessary resources for diagnosis A04.7 should be encouraged to reshape structural limitations and reprogram financial resources annually in a way that prioritizes the most effective approaches to treating patients with as few recurrent episodes of illness as possible.
6. Prevention of recurrent episodes of illness must be at the center of daily patient care, and in this way, the most cost-effective treatment strategy can be identified.

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