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CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA IN THE CLINICAL CENTER OF VOJVODINA, SERBIA, IN THE PERIOD 2008 TO 2012

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Abstract - *Clostridium difficile*-associated diarrhea (CDAD) has been recognized as the leading cause of diarrhea worldwide. In the last five years, it has become the leading cause of diarrhea in the Clinical Center of Vojvodina (CCV) as well. The aim of this study was to determine the epidemiology and total cost of treatment for all patients with *Clostridium difficile*-associated diarrhea hospitalized at the Infectious Disease Clinic of the CCV; to analyze the costs of treatment with regard to therapeutic approach; to compare the costs of treatment in each year of the investigated period related to the number of patients, and to analyze the outcome of treatment. The study was retrospective, and the data were collected from the medical records of 472 patients with *Clostridium difficile* diarrhea treated from 2008 to 2012 and analyzed. Of the total 472 patients with CDAD, 54.23% were female and the average age was 65.84. A statistically significant majority of them had been previously treated in other hospitals and a minority in ambulatory settings (395 inpatients vs. 77 outpatients, $p=0.000$, $p<0.05$). Of the 395 previously hospitalized patients, most were from the Clinic of Urology of the CCV (58, 14.68%). When comparing therapeutic options, oral vancomycin was significantly more frequently used than other protocols. The average mortality rate during the study period was 6.51%. In this period, total hospital costs related to *Clostridium difficile* diarrhea in the Infectious Disease Clinic were $636,679.92. Implementation of infection-control measures and a restricted use of antibiotics would result in a great reduction in material costs.

Key words: Clostridium difficile, costs, therapy

INTRODUCTION

Clostridium difficile-associated diarrhea (CDAD) has been recognized as the leading cause of diarrhea in healthcare settings worldwide. In the last five years, it has become the leading cause of diarrhea in the Clinical Center of Vojvodina (CCV) as well. It is also rapidly spreading outside hospitals and becoming a common cause of diarrhea in the community (Lo Vecchio et al., 2012).

Clostridium difficile (CD) is a gram-positive, anaerobic, spore-forming bacillus. It is responsible for different clinical presentations varying from the asymptomatic carrier state to fulminant colitis with toxic megacolon and perforation (Vaishnavi, 2010).

Clostridium difficile is identified as the cause of 15-20% of all antibiotic-associated diarrheas. In the last decades, the total number of *Clostridium difficile* infections (CDI) has increased, along with the number of cases with severe and fatal complications. Incidence and severity has dramatically increased since the appearance of a hypervirulent strain in 2000, especially in healthcare settings. The emergence of hypervirulent strains, coupled with indiscriminate use

of antimicrobials and inadequate infection control measures in hospitals are the primary factors contributing to the recent *C. difficile* outbreaks (Vermaet et al., 2011). Infection control in healthcare settings includes preventing the spread of infection (proper hand hygiene, use of personal protective equipment, environmental decontamination, isolation or cohort nursing and adequate treatment of CDAD cases.

This virulent strain has been associated with increased production of toxins A+B, fluoroquinolone resistance, and the production of binary toxin. The role of binary toxin is not clear but it may synergistically increase the virulence of toxins A and B. Based on data from the Centers of Disease Control and Prevention, the virulent strain NAP1/027 has been reported in most states throughout the US and in several countries in Europe. In the most recent data from European studies, the mean incidence of healthcare-associated CDI is 4.1 per 1 000 inpatient days (Bauer et al., 2011). In US population studies, CDI incidence rates range from 6.9 to 46 per 100 000 persons/year (Lo Vecchio et al., 2012).

The high costs attributable to CDI produce a substantial burden on healthcare systems worldwide (Verma et al., 2011). In US-based studies, estimated costs ranged from $2,871 to $4,846 per case for primary CDI and from $13,655 to $18,067 per case for recurrent CDI. US-based studies in special populations (subjects with irritable bowel disease, surgical inpatients, and patients treated in the intensive care unit) showed that additional costs were needed, ranging from $6,242 to $90,664. Non-US-based studies showed an estimated cost of $5,243 to $8,570 per case for primary CDI and $13,655 per case for recurrent CDI. In both primary and recurrent cases of CDI, economic healthcare costs are high. These costs related to CDI justify the use of additional resources for CDI prevention and control (Ghantoji et al., 2010). Successful prevention of CDAD in healthcare settings can be achieved by comprehensive infection control measures, including appropriate antimicrobial use, enforcement of infection control practices and better environmental cleaning (Eckstein et al., 2007).

Preventing healthcare-associated infections, including CDAD, would be beneficial to the whole of society. However, preventive measures can be expensive. In order to support these preventive efforts, it is important to gain better insights into the outcomes of CDAD (Perencevich et al., 2007).

Our aim was to estimate the total costs of CDI treatments for all patients at the Infectious Diseases Clinic, Clinical Center of Vojvodina, between 2008-2012, to present and compare the costs of treatment for patients with CDI taking into account the therapeutic approach, type of health facility where the patient had been previously treated or infected by *C. difficile* (comorbidities), and to analyze the costs over the years due to the number of patients and outcome of treatment.

MATERIALS AND METHODS

The study was a retrospective case study in which data collected from the medical records of all patients with CDI at the Infectious Diseases Clinic of the Clinical Center of Vojvodina in Novi Sad from 2008 to 2012, were analyzed; 472 patients with *Clostridium difficile* infection were investigated. The diagnosis of *Clostridium difficile*-associated diarrhea was based on laboratory identification of toxin A and/or B by toxin enzyme immunoassays (ELISA).

The following data were collected for all patients: patient demoFig.ics (age, gender), length of stay, previous hospitalization, therapeutic protocol used for treatment of initial episode and recurrence, length of hospitalization, total hospital cost and outcome of therapy.

All financial parameters are converted to US dollars using the official currency exchange rate of the National Bank of Serbia (NBS) in 2013 (on 19.04.2013, 1 $=85.11 RSD): the inflation rate in 2013 was also taken into consideration

RESULTS

Of the 472 study patients with CDI, 45.76% were

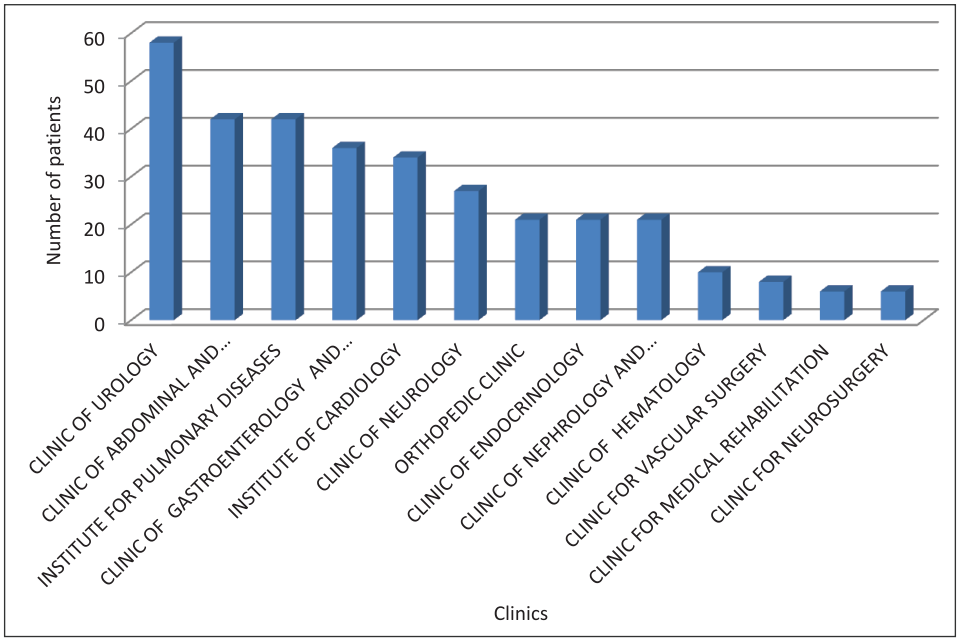

Fig. 1. Clinics where patients with *Clostridium difficile*-associated diarrhea were previously treated.

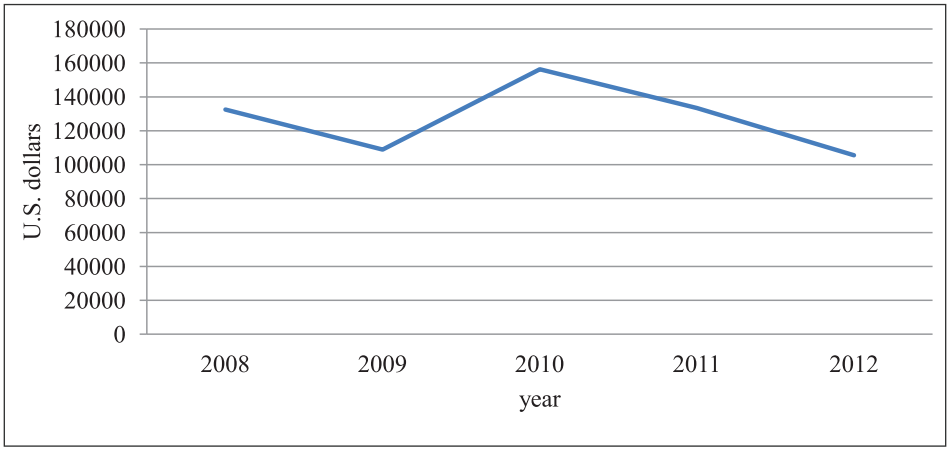

Fig. 2. Total hospital costs related to presence of *Clostridium difficile* infection from 2008 to 2012 at the Infectious Diseases Clinic, Clinical Center of Vojvodina.

male and 54.23% were female (p=0.31; p>0.05). The average age was 65.84; the youngest was 2 years old and the oldest patient was 92 years old.

A statistically significant majority of the patients had been previously treated in other hospitals and the minority in ambulatory settings (395 inpatients vs. 77 outpatients, p= 0.00, p <0.05). Among the 395 previously hospitalized patients, 58 (14.68%) were infected by *C. difficile* at the Clinic of Urology, 42 (10.63%) at the Clinic of Abdominal and Transplantation Surgery, 42 (10.63%) at the Institute for Pulmonary Diseases, 36 (9.11%) patients at the Clinic of Gastroenterology and Hepatology, 34 (8.6%) at the Institute of Cardiology, 27 (6.83%) at the Clinic of Neurology, 21 (5.31%) at the Orthopedic Clinic, Clinic of Endocrinology, Clinic of Nephrology and Immunology, 10 (2.53%) at the Clinic of Hematology, 8 (2.02%) at the Clinic

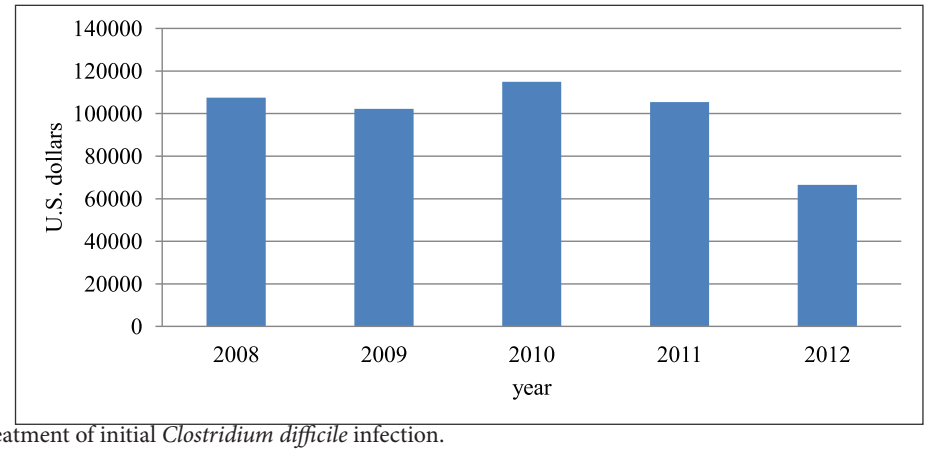

Fig. 3. Costs of treatment of initial *Clostridium difficile* infection.

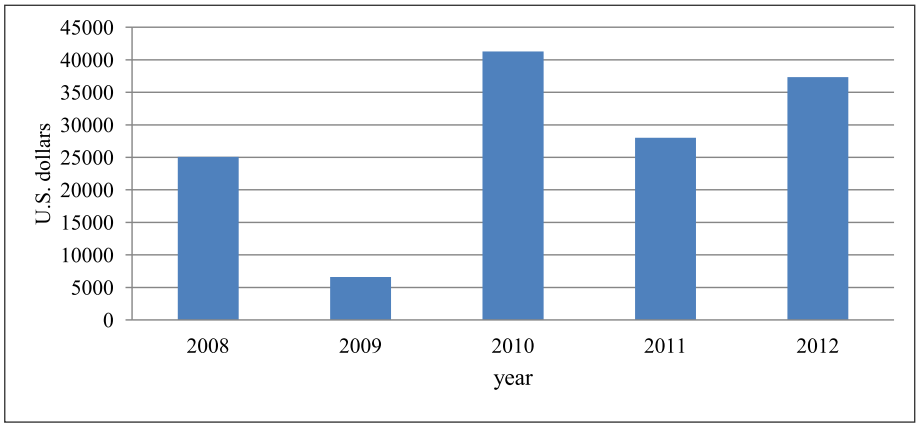

Fig. 4. Costs of treatment of recurrent *Clostridium difficile* infection.

for Vascular Surgery, and 6 (1.51%) at the Clinic for Medical Rehabilitation and Clinic for Neurosurgery, CCV (Fig. 1), while other health facilities were represented in lower percentages.

Total hospital costs related to presence of CDI in the period from 2008 to 2012 at the Infectious Diseases Clinic, Clinical Center of Vojvodina, were$ 636,679.92 (Fig. 2). The total hospital costs of treatment for CDI patients in 2008, 2009, 2010, 2011 and 2012 were $132,592.65, $108,887.78, $156,232.99, $133,445.15 and $105,521.35 respectively. The highest cost for the treatment of a single patient was $7,534.

Total hospital costs of treatment of initial CDI were $496,667.80 (Fig. 3).

Total hospital costs of treatment of recurrent CDI were $138,374.99 (Fig. 4). The *average cost of treatment* per case of initial *CDI* was about $1,149.03 and $1,081.74 for recurrent CDI (p=0.14, p>0.05). The *average cost of treatment* per day of *CDI* was about $1,131.90. There was no statistically significant difference between the average cost of treatment per day of initial and recurrent CDI ($97.19 vs. $103.47, p=0.67, p> 0.05). In the investigated five-year period, the highest total costs for the treatment of CDI patients were found at the Clinic of Urology, CCV, and came to $97,456.42 (15.13%).

Of the 472 cases, for the treatment of the initial episode of CDI, in 88 (18.64%) metronidazole in a dose 400-500 mg was given orally 3 times daily, 63 patients (13.34%) were treated with oral vancomy-

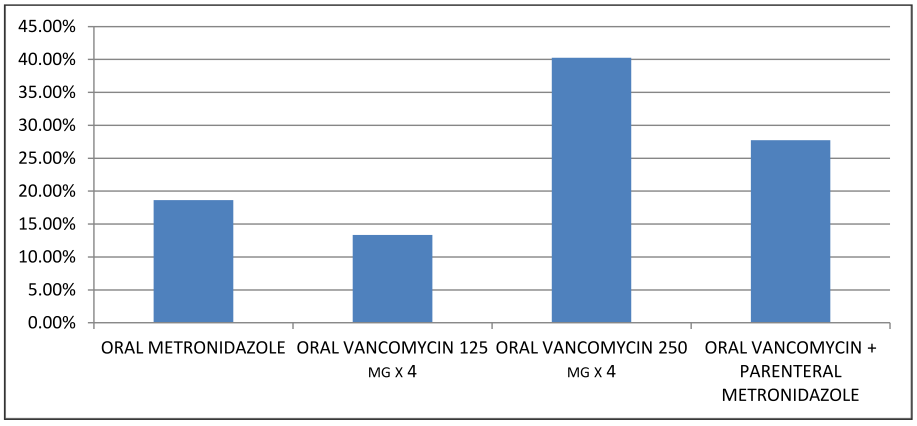

Fig. 5. Therapeutic options for initial *Clostridium difficile* infection.

Table 1. Costs of ten-day antimicrobial treatment of initial *Clostridium difficile* infection.

Therapeutic protocols	Cost of ten-day treatment (US dollars)
Oral dose of 440 mg metronidazole 3 times daily	3.44
Oral dose of 125 mg vancomycin 4 times daily	24.49
Oral dose of 250 mg vancomycin 4 times daily	48.98
Combined therapy with oral dose of 500 mg vancomycin daily and 500 mg parenteral metronidazole 3 times daily	172.93

cin in a dose of 125 mg 4 times daily, 190 (40.25%) were treated with oral vancomycin in a dose of 250 mg 4 times daily, and 131 (27.75%) were treated with a combination therapy of oral vancomycin and parenteral metronidazole. Comparing the therapeutic options, the significantly prevailing therapeutic protocol was oral vancomycin in a dose of 250 mg 4 times daily ($p = 0.00$, $p < 0.05$) (Fig. 5).

Ten-day costs for initial CDI with oral metronidazole in the CCV were $3.44, which is significantly lower than the oral vancomycin therapy option in a dose of 125 mg 4 times daily ($p<0.000$, $p<0.05$). The therapeutic option with oral vancomycin in a dose of 250 mg 4 times daily that costs $48.98 is statistically significantly more expensive compared to the treatment option with oral vancomycin in a dose of 125 mg 4 times daily, which costs $24.49 ($p<0.000$, $p<0.05$) (Table 1). Recurrent *C. difficile* infection occurred in 124/472 (26.27%) patients. There was no significant difference between mean length of stay in the initial episode of CDI compared to recurrent CDI (12.13 vs. 12.32, $p=0.96$, $p>0.05$). Mortality rates in 2008, 2009, 2010, 2011 and 2012 were 11 (11.11%), 8 (10.38%), 4 (3.66%), 4 (3.96%) and 3 (3.48%), respectively. Mortality rates were significantly higher in 2008 and 2009 compared to 2010, 2011 and 2012 ($p =0,046$, $p<0.05$). The average mortality rate during the study period was 6.51%.

DISCUSSION

Clostridium difficile-associated diarrhea is the most common cause of nosocomial diarrhea. The incidence and severity are constantly rising (Ricciardi et al., 2007). The epidemiology of CD infection has radically changed in the last decade (Deneve et al., 2009), which could be partly a result of the new and virulent strain of CD labeled NAP-01 (North American Pulsed-Field Type 1) ribotype 027 (Vermaet et

al., 2011), but the changes in the epidemiology of CDI also occurred in countries where the incidence of this strain was relatively low (Kovačević, 2012). There are neither data on presence of this *C. difficile* strain in our country, nor official epidemiological reports about the rate of incidence.

Our investigation included 472 patients hospitalized from 2008-2012 at the Clinic of Infectious Diseases with confirmed diagnosis of diarrhea caused by *Clostridium difficile.* A total of 99 patients were hospitalized in 2008, 77 patients were hospitalized in 2009, 109 in 2010, 101 in 2011 and 86 in 2012. We detected a statistically significant increase in number of hospitalized patients in 2010 compared to 2009 ($p = 0.01$). Despite the fact that the majority of the patients treated at the Clinic for Infectious Diseases suffered from CDI, only a few cases (i.e. 7 patients) were registered at the Clinic during the five-year period of monitoring.

Until five years ago, hospitalized patients with a diagnosis of diarrhea caused by CD in the Clinical Center of Vojvodina were sporadic, but from 2008-2012 the rising number of cases became a major concern, which corresponds to the recent epidemiological data in the world literature. With the appearance of the new strain, the incidence in Europe started rising, first in England, then in Ireland, Netherlands, Belgium, Luxembourg and France (Stevens et al., 2011).

Our demographics data showed that the average age of the patients was 65.84 and that 54.23% of patients were female. This corresponds to the data from literature that the frequency and severity of the disease increases in the population over 65 years. This population is at high risk because of recurrent hospitalizations and comorbidities. Studies have also confirmed the prevalence of females with CDI (King et al., 2011, Cohen et al., 2010. The factors that significantly increase the risk of CDI include the use of antibiotics, length of hospital stay, previous hospitalizations, surgical procedures, comorbidities and treatment with antacids (Hensgens et al., 2012).

Statistically significantly more patients were previously treated in a hospital, compared to outpatients (395 vs. 77, $p= 0.000$, $p <0.05$). Among 395 patients previously treated at another healthcare facility where they acquired *Clostridium difficile,* the majority came from the Clinic of Urology – 58 patients (14.68%), 42 (10.63%) at the Clinic of Abdominal and Transplantation Surgery, 42 (10.63%) at the Institute for Pulmonary Diseases, and 36 (9.11%) at the Clinic of Gastroenterology and Hepatology in the CCV. These data are difficult to compare with other studies because in our study the majority of patients with CDI were treated at the Infectious Diseases Clinic and not in the healthcare facilities where the infection had occurred. This policy at the Clinical Center of Vojvodina is the result of insufficient means to provide suitable patient isolation and implementation of appropriate measures for infection control and prevention. In most countries, patients are treated in the healthcare facilities where the infection was acquired (Centers for Disease Control and Prevention (CDC), 2012).

CDAD are diseases with significant financial impact (Stefan-Mikić et al., 2011). In the last five years, the occurrence of CDI is raising concerns in the CCV and requires the reevaluation of patient treatment costs and the economic consequences of this occurrence. In our study, we showed the material costs of treatment in the initial episode of CDI and in recurrent infections. Total material costs include the cost of laboratory tests and diagnostic procedures, costs of antimicrobial therapy, drug therapy for comorbidities and the cost of sanitary and medical staff expenditure.

Total hospital costs related to the presence of CDI in the period from 2008 to2012 at the Infectious Diseases Clinic, CCV, were $ 636,679.92. The total hospital costs of treatment for CDI patients in 2008, 2009, 2010, 2011 and 2012 were $132,592.65, $108,887.78, $156,232.99, $133,445.15 and $105,521.35 respectively. The highest cost for the treatment of a single patient reached $7,534. In this five-year period, the greatest costs for CDI therapy were registered at the Clinic of Urology and they amounted to $58,090.61 (10.93%).

The average cost of treatment per case of initial *CDI* was about $1,149.03 and $1,081.74 for recurrent CDI (p=0.14, p>0.05). The average cost of treatment per day of *CDI* was about $1,131.90. There was no statistically significant difference between the average cost of treatment per day of initial and recurrent CDI ($97.19 vs. $103.47, p=0.67, p> 0.05).

The coverage and structure of the CDI treatment costs vary from country to country. Different study designs, different numbers of patients and size of medical facilities as well as varieties in medical health systems worldwide make these data hard to compare. All studies in the last decade emphasize the significantly higher average cost of treating patients with CDI compared to other non-CDI patients and confirm that nosocomial CDAD is associated with 85% higher average costs (Pakyz et al., 2011).

Cumulative annual hospital healthcare costs due to *C. difficile* disease are estimated to be $1.1 billion in the US and in Europe the annual cost is estimated to $3 billion (Schneider et al., 2007). According to our knowledge, we do not have official data on the total material cost of CDI treatment in Serbia.

A treatment protocol with oral vancomycin in a dose of 250 mg four times a day compared to other treatment protocols (p = 0.000, p <0.05) was significantly more often used, because the majority of patients had already terminated one course of metronidazole therapy before admission to the Infectious Diseases Clinic. Results from clinical studies in the nineties of the last century, established metronidazole as a first line therapy in the treatment of initial episodes of CDAD due to its significantly lower price and similar clinical efficacy compared to vancomycin. However, recent clinical studies advocate vancomycin as the drug of choice in the treatment of severe CDAD (Vaishnavi, 2010). According to the latest IDSA guidelines (Infectious Disease Society of America) (Cohen et al., 2010) as well as European Society of Clinical Microbiology and Infectious Diseases guidelines (ESCMID) (Bauer et al., 2009), the treatment choice for the initial episode of CDI depends on the severity of the disease.

There was no significant difference between mean length of stay for initial episode of CDI and length of stay in recurrent CDI in our study (12.13 vs. 12.32, p=0.96, p>0.05). Cheng et al. (2011) presented data on the average length of hospital stay for the initial CDI of 8.7 days, and length of hospitalization for recurrent CDI of 13.6 days, which corresponds to the results of our study.

Recurrent CDI occurred in 26.27% of our patients, which correlates with literature data where 15-55% of patients with a good therapeutic response after the initial episode of CDI develop a recurrent form. The mortality rate during the study period was 6.51%, which corresponds to the data from US literature where the mortality rate was about 9.4% (Stewart et al., 2011).

In order to decrease the incidence and cost of treating patients with CDI, the Society for Healthcare Epidemiology of America (SHEA) and Infectious Disease Society of America (IDSA) issued clinical guidelines recommending a reduction in frequency and duration of antibiotic therapy as well as implementation of infection control measures such as isolation of infected persons, proper handling of the patient and disinfection of contaminated surfaces with 10% chlorinated disinfectants (Cohen et al., 2010 and Bauer et al., 2009).

CONCLUSION

Total hospital costs related to presence of CDI in period from 2008 to 2012 at the Infectious Diseases Clinic, Clinical Center of Vojvodina, were $ 636,679.92. The highest material costs for treatment of CDI patients in the period from 2008-2012, and were registered at the Clinic of Urology. The therapeutic protocol commonly used for the treatment of initial CDI is a ten-day treatment with oral vancomycin at a dose of 250 mg four times a day, and its cost is $4,276.80. The average mortality rate during the study period was 6.51%. Infection control measures and the control of antibiotic use would significantly reduce material costs for the treatment of this disease and allow for the redirection of material resources

within the healthcare system.

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