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Please cite this article: **RISK FACTORS FOR RECURRENT CLOSTRIDIUM DIFFICILE INFECTION AMONG PATIENTS IN CLINICAL CENTRE OF VOJVODINA, SERBIA: RETROSPECTIVE CLINICAL TRIAL**

**FAKTORI RIZIKA ZA POJAVU RELAPSA CLOSTRIDIUM DIFFICILE INFEKCIJE U KLINIČKOM CENTRU VOJVODINA, SRBIJA: RETROSPEKTIVNA KLINIČKA STUDIJA**

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UDC:

DOI: https://doi.org/10.2298/VSP170321119K

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
Risk factors for recurrent Clostridium difficile infection among patients in Clinical Centre of Vojvodina, Serbia: retrospective clinical trial

Faktori rizika za pojavu relapsa Clostridium difficile infekcije u Kliničkom centru Vojvodina, Srbija: retrospektivna klinička studija

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Abstract
Background/Aim: In the last two decades the incidence of recurrent Clostridium difficile infection (CDI) has risen. We aimed to determine the risk factors for recurrent CDI among patients hospitalized with initial CDI. Methods: We conducted a retrospective clinical trial at the Clinic for Infectious Diseases, Clinical Center of Vojvodina, Serbia, between January 2010 and January 2016. We enrolled 488 patients with initial CDI who were treated with oral vancomycin (125 mg 4 times per day) or oral metronidazole (400 mg 3 times per day) for 10 days. After completion of therapy there was a 60 days follow-up period for assessment the rates of relapse. To determine the risk factors for CDI relapse, we compare the demographics, clinical and laboratory characteristics of patients who had a relapse with patients who had stable clinical response. Results: Of the 488 cases, 29.09% recurred. The relapse occurred in 22.72% patients who received vancomycin, and in 36.60% patients treated with metronidazole (p=0.038). Statistically significant effect on the CDI relapse have comorbidities such as malignancies (19.52% vs 8.82%, p=0.023) and postoperative CDI (25.67% vs 10.29%, p=0.035), hipoalbuminemia (<25g/l) (70.27% vs 41.94%; p=0.034), concomitant antibiotic therapy (50.67% vs 20.29%; p=0.031). The persistence of C. difficile toxin in the stool at the end of treatment is registered with 22.32% of patients treated with metronidazole vs 9.09% of patients given vancomycin (p=0.03). Conclusions: Our data suggest that important risk factors for CDI relapse are comorbidities (surgery within a month before developing CDI and malignancy), hipoalbuminemia (<25g/l) and concomitant non-CDI antibiotics therapy. Vancomycin is more effective than metronidazole in the elimination of C. difficile toxins. The presence of C. difficile toxins in the stool after the successful completion of initial CDI therapy does not affect significantly the occurrence of relapse. Keywords: Clostridium difficile infection; risk factors; relapse
Apatrakt

Uvod/Cilj: Incidenca relapse Clostridium difficile infekcije (CDI) je u poslednje 2 decenije u porastu. Cilj rada je bio utvrđivanje faktorarizikazarelapskodbolesnikasainicijalnom CDI.

Metodologija: Na KlinicizainfektivnebolestiKliničogcentraVojvodine u Novom Sadu provedena je retrospektivnastudijau period od januara 2010 do januara 2016. Studijom je obuhvaćeno 488 pacijenatasainicijalnom CDI kojisulečeniperoralnim vankomicinom (125mg 4 puta dnevno) ili peroralnim metronidazolom (400 mg 3 puta dnevno) 10 dana. Nakon završene terapije bolesnici su praćeni 60 dana u cilju utvrđivanja pojave relapsa. U cilj uidentifikacijefaktor arizik azarelaps CDI upoređivanesudemografskie, kliničke, laboratorijske karakteristikebolesnikasarelapsu u odsunabolesnikesastabilnim kliničkimogovorom.

Rezultati: Relaps CDI je registrovankod 142/488 (29,09%) bolesnika od kojih je 22,72% lečeno vankomicinom i 36,60% lečenometronidazolom. StatističkiznačajanuticajnarelapsCDI suimalikomorbiditetikaoštosumalignaoboljenja (19.52% vs 8.82%, p=0.023) ipostoperativna CDI (25.67% vs 10.29%, p=0.035), hipoalbuminemija (<25g/l) (70.27% vs 41.94%, p=0.034), konkomitantna antibiotskaterapija (50.67% vs 20.29%, p=0.031). Perzistencija C. difficile toksina u stolicipozavršenoterapiji je registrovanakod 2.32% bolesnikalečenihmetronidazolom I 9,09% bolesnikalečenih vankomicinom (p=0.03). Prisustvotoksina C. difficile u stolicinakonaposavrelapsCDI nijeuticalosignifikantnonapojavurelapsa. Zaključak: Naširezultatipokazuju da faktorarizikazarelaps CDI predstavljaju komorbiditeti (postoperativna CDI, maligniteti), hipoalbuminemija i konkomitantna primena antibiotika. Vankomicinjeefikasni u eliminacijitoksina C. difficile iz kolona. Prisustvotoksina C. difficile u stolicinakonaposavrelapsCDI nijeuticalosignifikantnonapojavurelapsa.

Ključne reči: Clostridium difficile infekcija; faktor rizika, relaps
Introduction. The appearance of modern broad-spectrum antibiotics and other therapeutic agents has led, in the second half of the XX\textsuperscript{th} century, to an increase in the incidence of their adverse effects. This ascertainment especially refers to \textit{Clostridium difficile} infection (CDI), which is today the most common form of nosocomial diarrhea due to favorable conditions for the transmission of disease in hospitals and the presence of vulnerable population in them\textsuperscript{1}.

Particularly serious clinical and therapeutic problem is recurrent CDI. Although patients with an initial episode of CDI in most cases show a good response to therapy, 15-55\% of them develop recurrent form of the disease\textsuperscript{2,3}. The problem of recurrent CDI becomes increased by the fact that the first relapse is a significant predictor for new relapses. In pathophysiological terms CDI involves complex interaction between factors of the host, antibiotic activity and virulence of the pathogen. The cause of recurrent infections lies in the fact that no antibiotic eliminates \textit{C. difficile}(CD) spores from the intestinal tract. After successful treatment response in the initial episode of disease, endogenous spores in a reduced protective bacterial flora of the intestinal tract, transform themselves by germination into the vegetative forms that produce toxins and again lead to the development of diarrhea\textsuperscript{2,3,4}. The severity and frequency of CDI has increased rapidly in the last two decades, especially in the population of patients over 65 years. This is due to the fact that most people in this age category are immunocompromised as well as that intestinal microflora of bifidobacteria, which is considered protective, naturally declines in old age\textsuperscript{1,5}. Studies have also shown that certain comorbid diseases, leukocytosis, hypoalbuminemia, the degree of renal insufficiency, concomitant use of antibiotics, immuno-suppressants and proton pump inhibitors carry with them an increased risk of occurrence of CDI relapse\textsuperscript{2,3,5}. The impact of recurrent CDI on the whole health system becomes increasingly important because, by repeated episodes of disease extends the average duration of hospitalization and significantly increase the costs of treating patients.

As the current clinical trials in recent years recorded an increase in incidence of CDI relapse, there comes to the need for clearer defining of predictors that would indicate a
possible occurrence of relapse and accordingly for application of the appropriate therapy for high risk population of patients.

**Aim.** In this study we aimed to identify risk factors (RF) associated with relapse of CDI among patients hospitalized with initial CDI.

**Material and methods**

We conducted a retrospective clinical trial at the Clinic for Infectious Diseases, Clinical Center of Vojvodina, Serbia, between January 2010 and January 2016. We enrolled 488 patients with initial CDI who were treated with oral vancomycin (125mg 4 times per day) or oral metronidazole (400 mg 3 times per day) for 10 days. After completion of therapy, there was a 60 days follow-up period for assessment the rates of relapse. To determine RF for CDI relapse, we compare the demographics, clinical and laboratory characteristics of patients who had a relapse of CDI (case patients) with patients who have a stable clinical response (control patients).

CDI was defined as diarrhoea (defined as three or more unformed stools per day for at least 2 consecutive days) with positive CD toxin assay from faeces. Relapse was defined as a new episode of CD toxin positive diarrhea within 60 days after completion of therapy. Toxin was confirmed by the ELISA, RIDASCREEN C. difficile Toxin A and B (C0801), R-Biopharm AG, Germany. Stool samples were taken for analysis of CD toxins within 48 hours after hospitalization, after completion of CDI treatment, and any time of suspected recurrence of CD diarrhea. All stool specimens from our study patients were cultured for Salmonella, Shigella, Yersinia enterocolitica and Campylobacterspecies to exclude other infectious causes of diarrhea.

Criteria for inclusion in the study were: age > 18 years, a history of ongoing diarrhoea, positive CD toxin assay from stool samples within 3 days prior to hospitalization or positive stool sample collected for testing within 48h after hospitalization. Patients with diarrhea due to another known cause unrelated to CDI were excluded from the study. Data abstracted from the medical records included demographics information (age, gender), clinical information (dates of diarrhea onset and resolution, stooling frequency, fever), the presence of a chronic underlying illness (diabetes mellitus, chronic respiratory disease, chronic renal failure, liver disease, cardiovascular disease, malignancy, neurological
disease and surgery within a month before developing CDI), history of concomitant medications of importance (antibiotics and proton pump inhibitors during the treatment of initial CDI). Laboratory parameters of the initial CDI episode (peripheral leucocyte count, serum creatinine levels, albumin levels, serum C-reactive protein), were obtained within 48 hours of hospitalization. Follow-up period was 60 days after completion of therapy. In order to monitor the occurrence of relapses after discharge from the clinic, follow-up visits were carried out 20, 30 and 60 days after completion of therapy. During those visits, anamnestic data and physical examination were performed and stool samples were taken for analysis of CD toxins any time of suspected CDI relapse.

**Statistical analyses**

Statistical analysis was performed with the statistical package SPSS version 13.0. The descriptive statistical parameters are shown in standard statistical variables, arithmetic mean (X), standard deviation (SD), interval values (maximum and minimum). Testing statistical significance was determined for parametric data by ANOVA test (analysis of variance), and for non-parametric by X² test, Fisher's or Mann Whitney's test. For all tests of statistical significance, the level of trust was p< 0.05. The results are shown by absolute numbers, percentages, in tables and graphics, followed by text comments.

**Results**

During the study period, we diagnosed 142/488 (29.09%) of patients with first relapse of CDI. The relapse occurred in 60/264 (22.72%) patients who received vancomycin, and in 82/224 (36.60%) patients treated with metronidazole (p=0.038) (table 1).

**Risk factors for recurrence.** In our analysis, age (p=0.26) and sex (p=0.40) did not have statistically significant effect on the CDI relapse occurrence. Most of the patients were of the age category of over 65 years in both groups of patients (69.34% of patients with stable clinical response and 75.22% of patients with relapse) (table 2). With regard to the clinical characteristics of the patients in first CDI episode, case and control patients did not differ significantly in terms of presence of fever (p=0.69) and maximum stooling frequency (p=0.34) but duration of diarrhea during the treatment of the first episode of CDI had a statistically significant effect on relapse occurrence (p=0.016). The patients had a stable clinical response if the average duration of diarrhea after initiation of
therapy was $\overline{X} = 4.45 \pm 3.14$ SD days, while the relaps was registered in patients with the average duration of diarrhea of $\overline{X} = 8.32 \pm 6.21$ SD days ($p = 0.016$) (table 2).

Analysis of the comorbid conditions at the occurrence of CDI relapse has shown that malignant diseases and surgery within a month before developing CDI have statistically significant effect on the CDI relapse. We found that $32/346 (8.82\%)$ of patients with malignant diseases had a stable clinical response compared to $29/142 (19.52\%)$ of patients with relapse ($p = 0.023$). Total $36/346 (10.29\%)$ of patients with postoperative CDI had a stable clinical response versus $38/142 (25.67\%)$ of patients with relapse ($p = 0.035$). Other comorbid conditions did not have statistically significant effect on the relapse occurrence.

Laboratory parameter with a statistically significant impact on occurrence of CDI relapse is low albumin level ($<25g/l$). Total $146/346 (41.94\%)$ of patients had a stable clinical response and $104/142 (70.27\%)$ of patients got a relapse ($p = 0.034$). High leucocyte count ($p = 0.37$) and creatinine level ($p = 0.28$) did not statistically significantly affect on the occurrence of CDI relapse.

It is known that concomitantly applied therapy during the first episode of CDI can have a statistically significant effect on relapse occurrence. We found that $69/346 (20.29\%)$ of patients on antibiotic therapy for concomitant disease had a stable clinical response, and $75/142 (50.67\%)$ of patients had relapse ($p = 0.031$). Concomitant use of proton pump inhibitors had no statistically significant effect on the CDI relapse (table 2).

**Microbiological data after treatment.** Through the study we also investigated the presence of CD toxins in the stool after successfully completed initial CDI treatment, and the impact of the toxins persistenc eon CDI relapse. We found that vancomycin is significantly better than metronidazole in clearing of CD toxins. After completion of therapy, the persistence of CD toxins is registered with $50/224 (22.32\%)$ of patients treated with metronidazole and with $24/264 (9.09\%)$ of patients treated with vancomycin ($p = 0.003$).

Patients treated with metronidazole, after successful elimination of CD toxins in stool have a stable clinical response in $115/142 (80.98\%)$ of cases while relapse developed in $56/82 (68.51\%)$ of patients. Patients with persistence of CD toxins in stool treated with metronidazole, develop relapse in $26/82 (31.71\%)$ of cases versus $27/142 (19.01\%)$ of patients with stable clinical response ($p = 0.08$). After successful elimination of CD toxins in stool, vancomycin therapy has led to a stable clinical response in $183/204 (89.71\%)$ of patients, and to relapse in $52/60 (86.67\%)$ of patients. If the CD toxins in the stool persisted
after the completed vancomycin therapy, the relapse was registered in 8/60 (13.33%) of patients and 21/204 (9.82%) of patients had stable clinical response \((p=0.16)\). The results showed that the presence of CD toxins in the stool after the successful completion of initial CDI therapy does not affect significantly the occurrence of relapse \((table 3)\).

**Discussion**

Due to the fact that relapse occurs after successfully completed therapy in 10-20% but when a patients has had one recurrence, rate of further recurrences increase to 40-65% i.e. each relapse is potential predictor for the development of new relapses, the need arose for a clearer identification of specific RF that are associated with the CDI relapse\(^5\). In our study, the occurrence of CDI relapse was observed in 29.09% of patients. Numerous studies have demonstrated the existence of a link between age and the CDI relapse occurrence\(^1,2,3,6,7\). Our study did not confirm this fact, probably because most of the patients were of the age category of over 65 years (69.34% of patients with stable clinical response and 75.22% of patients with relapse). Various therapeutic regimes applied in the treatment of first episode of CDI had a different impact on occurrence of CDI relapse. The frequency of relapses in patients who were treated with metronidazole in the initial episode of CDI was 36.60% \(vs\) 22.72% of the patients who got relapse after the treatment with vancomycin \((p=0.038)\). Contrary to our research, Lupșe et al. did not record statistically significant difference in the occurrence of relapses in these treatment groups\(^6\). Scheurer has demonstrated, similarly to our research that patients treated with metronidazole are more likely to develop relapse compared to patients treated with vancomycin (14% \(vs\) 7%, \(p<0.025\))\(^8\). Contrary to these results, Kim et al. have found a higher incidence of relapse after the therapy of vancomycin compared to metronidazole (41.2% \(vs\) 18.7%, \(p=0.054\)), but they stressed that with the vancomycin were treated significantly more patients with severe forms of CDI (52.9% \(vs\) 21.1%, \(p=0.009\))\(^9\).

According to the results of our research, specific comorbid states have a statistically significant impact on the occurrence of CDI relapse. After surgeries, relapse developed in 25.67% of our patients while stable clinical response had only 10.29% of patients \((p=0.035)\). Similarly to our research, the study of Jung has shown that surgical procedures are statistically significant predictor of CDI relapse after treatment with metronidazole \((p=0.032)\), and the research of Hsu et al. showed that postoperative CDI after organ transplantation has a statistically significant impact on the CDI relapse after the vancomycin.
therapy \((p=0.011) \) \(^{10,11}\). Increased risk of relapse in operated patients is mostly contributed by the state of malnutrition and immune deficiency occurring in the postoperative period, as well as the frequent use of antibiotics both before and during the postoperative period \(^ {12}\). The results of our study confirm a statistically significant impact of malignancies on the occurrence of CDI relapse. Relapse developed in 19.52\% of patients with malignant tumors, while stable clinical response had only 8.82\% of patients \((p=0.023)\). Studies have shown that patients with malignancies which require chemotherapy more often get CDI relapse independently of the use of antibiotics, almost with each cycle of chemotherapy. This is contributed by several factors such as: alteration of the intestinal microflora, severe inflammatory lesions of mucosa of the colon, induced by chemotherapy, intestinal necrosis, decreased degradation of CD toxin and the inability to regenerate normal intestinal flora. Taking into account the occurrence of oral-gastrointestinal mucositis and nausea caused by chemotherapy, these patients often poorly tolerate metronidazole and it is considered justified the initial implementation of vancomycin even in the easier forms of CDI in patients with malignant disease which requires the use of chemotherapy \(^{13,14,15}\).

In our finding a high peripheral leucocyte count \((>15000/mm^3)\) at onset of the initial CDI episode was not predictive of recurrent CDI which is contrary to results of Rodrigues et al\(^ {16}\). These authors suggest that patients with high leucocyte count had a more severe initial CDI episode which may leave the bowel more vulnerable to subsequent CDI. In our study hypoalbuminemia had statistically significant effect on the occurrence of CDI relapse. In patients with albumin level of \(<25\ g/l\), relapse developed in 70.27\% vs 41.94\% of patients with stable clinical response \((p=0.034)\). Similar to our results, Rotramel and Shakoval also proved a statistically significant effect of hypoalbuminemia on the occurrence of CDI relapse \(^ {17,18}\). These results are attributable to the fact that CD toxin-A increases vascular and mucosal permeability of intestinal tract resulting in intraluminal accumulation of fluid rich with serum albumin. Hypoalbuminemia is a marker of poor underlying health condition, a protracted associated chronic diseases, poor nutritional status and poor immune function of the host, and therefore the lack of production of toxin-neutralizing IgA antibodies to CD which may increase the risk for CDI \(^ {5,13,20}\).

We found that concomitant use of non-CDI antimicrobials during the first episode of CDI raise the risk for recurrent CDI. Frequency of CDI relapses compared to the stable clinical response was 50.67\% vs 20.29\% \((p=0.031)\). Kelly’s research also demonstrated that
The concomitant use of non-CDI antibiotics significantly affects the occurrence of CDI relapse \( p=0.0012 \) \(^{19} \). The authors of other studies came to the same conclusion\(^ {21-23} \). Antimicrobial therapy for the concomitant infections may result in an altered bowel microflora, favoring CD growth. More frequent occurrence of relapses due to concomitant use of antibiotics for conditions that are not related to CDI was due to higher level of additional continuous disruption of the intestinal flora, which allows persistence of CD\(^ {24,25} \). In our study was not shown statistically significant effect of the use of proton pump inhibitors on the occurrence of CDI relapse. Studies published by the Lupșe and Rodrigues demonstrated a statistically significant effect of proton pump inhibitors on the occurrence of CDI relapse, while Rotramel did not find that connection \(^ {6,16,17} \). Whether gastric acid suppression is truly an independent RF for recurrent CDI remains unknown.

**The effect of the elimination of CD toxins on the CDI relapse.** The results of our study showed that vancomycin is more effective than metronidazole in the elimination of CD toxins from the intestinal tract. After the completion of CDI therapy, the persistence of CD toxins was found in 22.32\% of patients treated with metronidazole compared to 9.09\% of patients given vancomycin \( p=0.003 \). Similarly to our results, research of McFarland found that vancomycin is significantly more efficient than metronidazole in the elimination of CD toxins from the colon. In this study, 11\% of patients treated with vancomycin versus 41.2\% of patients given metronidazole \( p=0.0004 \) were positive for CD toxins in the stool after completion of therapy \(^ {26} \). Wullt registered the persistence of CD toxins after treatment with metronidazole in 23\% of patients, and the study of De Lalla showed that after the treatment with vancomycin the persistence of CD toxins have 25\% of patients \(^ {27,28} \). Literature data indicate that post-therapy bacterial persistence is not conditioned only by applied therapy regime but also by a strain of CD, its capacity of toxin production and sporulation but also by factors of the host such as the presence of nutritional contents in the intestines which are crucial for toxin production and the state of the immune system, that is, the production toxin-neutralizing Ig A antibodies \(^ {28,29,30} \).

Previous studies have shown greater efficacy of vancomycin compared to metronidazole in the elimination of CD toxins from the colon, but studies has not proven the higher frequency of relapse in patients with the persistence of CD toxins \(^ {26,30} \). McFarland et al have shown that after metronidazole treatment, patients who had recurrences did not have a significantly higher frequency of CD persistence (53.5\%) than
those who did not have relapse (31.6%)\textsuperscript{26}. Norren et al have analyzed the link between microbial efficiency and clinical outcomes after CDI therapy with metronidazole and concluded that in the case of persistence of CD toxins, stable clinical response is achieved in 57\% of patients versus 74\% of patients with stable clinical response\textsuperscript{29}. In accordance with previous research, the results of our study also show that the presence of CD toxins in the stool, after the completion of CDI therapy, does not affect significantly the occurrence of relapse. In our study, persistence of CD toxins was registered in 13.87\% of patients with stable clinical response versus 23.94\% of patients with relapse (p > 0.05). After treatment with metronidazole this ratio was 19.01\% vs 31.71\% (p = 0.08), and after treatment with vancomycin 9.82\% vs 13.33\% (p = 0.16). This finding could be interpreted by the previously proven fact that asymptomatic carriers, after successfully completion of the initial episode of CDI, develop a sufficient level of toxin-neutralizing A antibodies to CD, by which this population of patients acquire low risk of CDI relapse. Therefore, in daily practice, after successfully completed treatment, is not recommended routine testing of stool samples on the presence of CD toxins as a “control test of treatment success.”\textsuperscript{30}

Our findings confirms that CDI is present in our settings with significant rate of relapse. The primary strength of our study is its ability to point out the population of patients at highest risk of CDI relapse in our settings, because almost all important RF of relapse mentioned in to date literature were taken into consideration. Besides, the study encompassed a significant number of patients and therefore we believe that our findings may be of great importance for the creation of future therapeutic strategies in CDI treatment. However, this study had several limitations. Firstly, it was retrospective clinical trial. Secondly, although we are aware that the host immune system plays crucial role in CDI relapse, we were not able to measure anti-toxin IgG levels in our patients. Furthermore, because of the rising prevalence of the epidemic CD strains that producing more severe disease and causing more frequent CDI relapse, the aim of some future investigation could also be to determine and analyze strains of CD in our settings.

In conclusion, our data suggest that important RF for CDI relapse are comorbidities such as a recent surgery (within a month before developing CDI) and malignancy, low albumin level (<25 g/l), as well as concomitant non-CDI antibiotics treatment. Future treatment strategies for CDI relapse should emphasize on those group of patients.
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<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Treatment regimen</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>metronidazole</td>
<td>vancomycin</td>
</tr>
<tr>
<td></td>
<td>n - 224</td>
<td>n – 264</td>
</tr>
<tr>
<td>Stabile clinical response</td>
<td>n 142</td>
<td>204</td>
</tr>
<tr>
<td></td>
<td>% 63.39%</td>
<td>77.27%</td>
</tr>
<tr>
<td>Relapse</td>
<td>n 82</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>% 36.60%</td>
<td>22.72%</td>
</tr>
</tbody>
</table>

Table 1. Treatment outcome
### Table 2. Characteristics of patients and treatment outcomes

<table>
<thead>
<tr>
<th>Patients characteristic</th>
<th>Stable clinical response n - 346</th>
<th>Relapse n - 142</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (≥65 years)</td>
<td>69,34%</td>
<td>75,22%</td>
<td>0.26</td>
</tr>
<tr>
<td>Gender (male : female)</td>
<td>61%:39%</td>
<td>58%:42%</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>32 (8,82%)</td>
<td>29 (19,52%)</td>
<td>0.023</td>
</tr>
<tr>
<td>Postoperative CDI*</td>
<td>36 (10,29%)</td>
<td>38 (25,67%)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>Clinical characteristic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of bowel movements ≥ 10 / 24h</td>
<td>139 (40,98%)</td>
<td>56 (37,83%)</td>
<td>0.34</td>
</tr>
<tr>
<td>Temperature ≥ 38°C</td>
<td>755 (22,05%)</td>
<td>28 (18,91%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Durations of diarrhea during treatment (\overline{X}) days ± SD</td>
<td>4,45 (± 3,14)</td>
<td>8,32 (± 6,21)</td>
<td>0,016</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin level &lt; 25 g/l</td>
<td>146 (41,94%)</td>
<td>104 (70,27%)</td>
<td>0.024</td>
</tr>
<tr>
<td>Leukocytosis ≥ 15000 /mm³</td>
<td>132 (38,82%)</td>
<td>62 (41,89%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Serum creatinine level ≥ 200 µg / l</td>
<td>48 (14,11%)</td>
<td>29 (19,59%)</td>
<td>0.28</td>
</tr>
<tr>
<td>C- reactive protein (\overline{X}) µg l ±SD</td>
<td>108,99 (±80,92)</td>
<td>157,13 (± 75,13)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>69 (20,29%)</td>
<td>75 (50,67%)</td>
<td>0.031</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>58 (17,05%)</td>
<td>22 (14,86%)</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>Microbiological data after treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clearance of CD toxins</td>
<td>298 (86,13%)</td>
<td>108 (76,05%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Persistence of CD toxins</td>
<td>48 (13,87%)</td>
<td>34 (23,94%)</td>
<td></td>
</tr>
</tbody>
</table>

*CDI – Clostridium difficile infection*
Table 3. Elimination of CD toxins after treatment and treatment outcomes

<table>
<thead>
<tr>
<th>Microbiological effect after treatment</th>
<th>metronidazole</th>
<th>vancomycin</th>
<th>p</th>
<th>metronidazole</th>
<th>vancomycin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>stable clinical response</td>
<td>relapse</td>
<td>n:142</td>
<td>stable clinical response</td>
<td>relapse</td>
<td>n:204</td>
</tr>
<tr>
<td>Clearance of CD toxins</td>
<td>n</td>
<td>115</td>
<td>56</td>
<td>183</td>
<td>52</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>80.98%</td>
<td>68.51%</td>
<td>89.71%</td>
<td>86.67%</td>
<td>0.16</td>
</tr>
<tr>
<td>Persistence of CD toxins</td>
<td>n</td>
<td>27</td>
<td>26</td>
<td>21</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>19.01%</td>
<td>31.71%</td>
<td>9.82%</td>
<td>13.33%</td>
<td></td>
</tr>
</tbody>
</table>

*CD – Clostridium difficile

Received on March 21, 2017.
Revised on May 07, 2017.
Accepted on July 12, 2017.
Online First September, 2017.