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Risk factors for recurrent *Clostridium difficile* infection among patients in the Clinical Centre of Vojvodina, Serbia: a retrospective clinical trial

Faktori rizika od pojave 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. The aim of this study was to determine the risk factors for the recurrent CDI among patients hospitalized with the 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 the 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 the completion of therapy, there was 60 days of the follow-up period for the assessment of the rates of relapse. To determine the risk factors for the CDI relapse, we compared the demographics, clinical and laboratory characteristics of the patients who had a relapse with the patients who had a stable clinical response. **Results.** Of the 488 cases, 29.09% recurred. The relapse occured in 22.72% patients who received vancomycin and in 36.60% patients treated with metronidazole (p = 0.038). A statistically significant effect on the CDI relapse had the comorbidities such as a malignancies (19.52% *vs* 8.82%, p = 0.023) and the postoperative CDI (25.67% *vs* 10.29%, p = 0.035), hipoalbuminemia (< 25 g/L) (70.27% *vs* 41.94%; p = 0.034) and the 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 was registered in 22.32% of patients treated with metronidazole *vs* 9.09% of patients given vancomycin (p = 0.03). **Conclusion.** Our data suggest that the important risk factors for the 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 the initial CDI therapy does not affect significantly the occurrence of relapse.

Key words:
clostridium difficile; infection; recurrence; risk factors.

Apstrakt

Uvod/Cilj: Incidenca relapsne *Clostridium difficile* infekcije (CDI) je u poslednje dve decenije u porastu. Cilj rada bio je utvrđivanje faktora rizika od relapsa kod bolesnika sa inicijalnom CDI. **Metode.** Na Klinici za infektivne bolesti Kliničog centra Vojvodine u Novom Sadu sprovedena je retrospektivna studija u period od januara 2010. do januara 2016. Studijom je obuhvaćeno 488 bolesnika sa inicijalnom CDI koji su lečeni peroralnim vankomicinom (125 mg, četiri puta dnevno) ili peroralnim metronidazolom (400 mg, tri puta dnevno) 10 dana. Nakon završene terapije bolesnici su praćeni 60 dana u cilju utvrđivanja pojave relapsa. U cilju identifikacije faktora rizika od relapsa CDI upoređivane su demografske, kliničke i laboratorijske karakteristike bolesnika sa relapsom u odnosu na bolesnike sa stabilnim kliničkim odgovorom. **Rezultati.** Relaps CDI je registrovan kod 142/488 (29,09%) bolesnika od kojih je 22.72% lečeno vankomicinom i 36.60% lečeno metronidazolom. Statistički značajan uticaj na relaps CDI su imali komorbiditet kao što su maligna oboljenja (19,52% *vs* 8,82%, p = 0,023) i postoperativna CDI (25,67% *vs* 10,29%, p = 0,035), hipoalbuminemija (< 25 g/L) (70,27% *vs* 41,94%, p = 0,034), konkomitantna antibiotska terapija (50.67% *vs* 20,29%, p = 0,031). Perzistencija *C. difficile* toksina u stolici po završenoj terapiji je registrovana kod 22,32% bolesnika lečenih metronidazolom i 9,09% bolesnika lečenih vankomicinom (p = 0,03). Prisustvo toksina *C. difficile* u stolici nakon uspešno završene terapije inicijalne CDI nije uticalo signifikantno na pojavu relapsa. **Zaključak.** Naši rezultati pokazuju da faktore rizika od relapsa CDI predstavljaju komorbiditeti (postoperativna CDI, maligniteti), hipoalbuminemija i konkomitantna primena antibiotika. Vankomicin je efikasniji u eliminaciji toksina *C. difficile* iz kolona.

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Prisustvo toksina *C. difficile* u stolici nakon uspešno završene terapije ne utiče signifikantno na pojavu relapsa.

Ključne reči:
clostridium difficile; infekcija; recidiv; faktori rizika.

Introduction

The appearance of modern broad-spectrum antibiotics and other therapeutic agents has led, in the second half of the 20th century, to an increase in the incidence of their adverse effects. This ascertainment especially refers to *Clostridium difficile* infection (CDI), which is today the most common form of nosocomial diarrhea due to favorable conditions for the transmission of the disease in hospitals and the presence of vulnerable population in them [1].

Particularly serious clinical and therapeutic problem is a recurrent CDI. Although the patients with an initial episode of CDI in most cases show a good response to therapy, 15% –55% of them develop the recurrent form of the disease [2, 3]. The problem of the recurrent CDI has increased because of 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 the *C. difficile* (CD) spores from the intestinal tract. After a successful treatment response in the initial episode of disease, the 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 [2–4]. The severity and frequency of CDI 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 [1, 5]. Relevant studies also showed that certain comorbid diseases, leukocytosis, hypoalbuminemia, the degree of renal insufficiency, concomitant use of antibiotics, immunosuppressants and proton pump inhibitors carry with them an increased risk of the CDI relapse [2, 3, 5]. The impact of the recurrent CDI on the whole health system becomes increasingly important because repeated episodes of the disease extend the average duration of hospitalization and significantly increase the costs of treating the patients.

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

The aim of this study was to identify risk factors (RF) associated with relapse of CDI among the patients hospitalized with the initial CDI.

Methods

CDI was defined as diarrhea (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 CD 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 the 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 Campylobacter* species to exclude other infectious causes of diarrhea.

The criteria for inclusion in the study were: age > 18 years, a history of ongoing diarrhea, positive CD toxin assay from stool samples within 3 days prior to hospitalization or positive stool sample collected for testing within 48 h after hospitalization. The 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 inhibitorsduring 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. A follow-up period was 60 days after the completion of therapy. In order to monitor the occurrence of relapses after discharge from the clinic, the follow-up visits were carried out 20, 30 and 60 days after the completion of therapy. During those visits, the 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 using the statistical package SPSS version 13.0. The descriptive statistical parameters were shown in the standard statistical variables, arithmetic mean ($\overline{x}$), standard deviation (SD), interval values (maximum and minimum). Testing a statistical significance was determined for the parametric data by the ANOVA test (analysis of variance), and for non-parametric data by the χ^2 test, Fisher's or Mann-Whitney test. For all tests the level of statistical significance, was $p < 0.05$.

Results

During the study period, we diagnosed 142/488 (29.09%) of patients with the first relapse of CDI. The re-

lapse occured 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 the stable clinical response and 75.22% of patients with the relapse) (Table 2). With regard to the clinical characteristics of the patients in the first CDI episode, the 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 the duration of diarrhea during the treatment of the first episode of CDI had a statistically significant effect on the relapse occurrence ($p = 0.016$). The patients had a stable clinical response if the average duration of diarrhea after initiation of therapy was 4.45 [± standard deviation (SD) = 3.14] days, while the relaps was registered in the patients with the average duration of diarrhea of 8.32 (± SD = 6.21) days ($p = 0.016$) (Table 2).

The analysis of the comorbid conditions at the occurrence of CDI relapse showed that malignant diseases and surgery within a month before developing CDI had a statistically significant effect on the CDI relapse. We found that 32/346 (8.82%) patients with malignancies had a stable clinical response compared to 29/142 (19.52%) patients with a relapse ($p = 0.023$). Total of 36/346 (10.29%) patients with postoperative CDI had a stable clinical response versus 38/142 (25.67%) patients with a relapse ($p = 0.035$). Other comorbid conditions did not have a statistically significant effect on the relapse occurrence. The laboratory parameter with a statistically significant impact on occurrence of the CDI relapse was low albumin level (< 25 g/L). Total 146/346 (41.94%) of patients had a stable clinical response and 104/142 (70.27%) patients got a relapse ($p = 0.034$). High leucocyte count ($p = 0.37$) and creatinine level ($p = 0.28$) did not statistically significantly affected 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 the relapse occurrence. We found that 69/346 (20.29%) patients on antibiotic therapy for concomitant disease had a stable clinical response, and 75/142 (50.67%) patients had the relapse ($p = 0.031$). Concomitant use of proton pump inhibitors had no statistically significant effect on the CDI relapse (Table 2).

Table 1

Treatment outcome in patients treated by different antibiotics

Treatment outcome	Metronidazole (n = 224)	Vancomycin (n = 264)	Total (n = 488)	*p*
	n (%)	n (%)	n (%)	
Stabile clinical response	142 (63.39)	204 (77.27)	346 (70.90)	0.038
Relapse	82 (36.60)	60 (22.73)	142 (29.10)	

Table 2

Characteristics of patients and treatment outcomes

Patients characteristic	Stable clinical response (n = 346)	Relapse (n = 142)	*p*
Demographics			
age (≥ 65 years), %	69.34	75.22	0.26
gender (male / female), n	61 / 39	58 / 42	0.40
Comorbidities, n (%)			
malignancy	32 (8.82)	29 (19.52)	0.023
postoperative CDI	36 (10.29)	38 (25.67)	0.035
Clinical characteristic			
no. of bowel movements ≥ 10/24 h, n (%)	139 (40.98)	56 (37.83)	0.34
temperature ≥ 38°C, n (%)	755 (22.05)	28 (18.91)	0.69
durations of diarrhea during treatment (days), mean ± SD	4.45 ± 3.14	8.32 ± 6.21	0.016
Laboratory data			
albumin level < 25 g/L, n (%)	146 (41.94)	104 (70.27)	0.024
leukocytosis ≥ 15,000/mm³, n (%)	132 (38.82)	62 (41.89)	0.37
serum creatinine level ≥ 200 μg/L, n (%)	48 (14.11)	29 (19.59)	0.28
C- reactive protein (μg L) mean ± SD	108.99 ± 80.92	157.13 ± 75.13	0.14
Concomitant medications, n (%)			
antibiotics	69 (20.29)	75 (50.67)	0.031
proton pump inhibitors	58 (17.05)	22 (14.86)	0.22
Microbiological data after treatment, n (%)			
clearance of CD toxins	298 (86.13)	108 (76.05)	0.12
persistence of CD toxins	48 (13.87)	34 (23.94)	0.09

***CDI – *Clostridium difficile* infection; SD – standard deviation.**

Table 3

Elimination of CD toxins after treatment and treatment outcomes

Microbiological effect after treatment	Metronidazole, n (%)			Vancomycin, n (%)		
	stabile clinical response (n = 142)	relapse (n = 82)	*p*	stabile clinical response (n = 204)	relapse (n = 60)	*p*
Clearance of CD toxins	115 (80.98)	56 (68.51)	0.08	183 (89.71)	52 (86.67)	0.16
Persistence of CD toxins	27 (19.01)	26 (31.71)		21 (9.82)	8 (13.33)	

CD – *Clostridium difficile.

Microbiological data after treatment

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

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

Discussion

Due to the fact that the relapse occurs after the successfully completed therapy in 10%–20% of patients, but when the patients had one recurrence, a rate of further recurrences increase to 40%–65%, i.e., each relapse is a potential predictor for the development of new relapses, there appears a need for a clearer identification of specific RF associated with the CDI relapse [5]. In our study, the occurrence of the CDI relapse was observed in 29.09% of patients. Numerous studies demonstrated the existence of a link between age and the CDI relapse occurrence [1–3, 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 a stable clinical response and 75.22% of patients with a relapse). Various therapeutic regimes applied in the treatment of the first episode of CDI had a different impact on occurrence of CDI relapse. The frequency of relapses in the patients who were treated with metronidazole in the initial episode of CDI was 36.60% *vs* 22.72% of the patients who had a relapse after the treatment with vancomycin ($p = 0.038$). Contrary to our research, Lupşe et al. [6] did not record a statistically significant difference in the occurrence of relapses in these treatment groups. Scheurer and Ross [8] demonstrated, similarly to our research, that the patients treated with metronidazole were more likely to develop relapse compared to the patients treated with vancomycin (14% *vs* 7%, $p < 0.025$). Contrary to these results, Kim et al. [9] 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 significantly more patients with severe forms of CDI (52.9% *vs* 21.1%, $p = 0.009$) were treated with vancomycin.

According to the results of our research, specific comorbid states have a statistically significant impact on the occurrence of CDI relapse. After surgeries, the relapse developed in 25.67% of our patients while the stable clinical response was found only in 10.29% of patients ($p = 0.035$). Similarly to our research, the study of Jung et al. [10] showed that the surgical procedures are statistically significant predictors of CDI relapse after the treatment with metronidazole ($p = 0.032$), and the research of Hsu et al. [11] showed that postoperative CDI after organ transplantation had a statistically significant impact on the CDI relapse after the vancomycin therapy ($p = 0.011$). An increased risk of relapse in the operated patients is mostly dependant on 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 confirmed a statistically significant impact of malignancies on the occurrence of CDI relapse. The relapse developed in 19.52% of patients with malignant tumors, while the stable clinical response had only 8.82% of patients ($p = 0.023$). Some studies showed that the patients with malignancies which require chemotherapy more often got the CDI relapse independently of the use of antibiotics, almost with each cycle of chemotherapy. Several factors may contributed to this and they are such as: alteration of the intestinal microflora, severe inflammatory lesions of mucosa of the colon, 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 tolerate metronidazole poorly and it is considered justified the initial implementation of vancomycin even in the easier forms of CDI in the patients with malignant disease which requires the use of chemotherapy [13–15].

In our findings, a high peripheral leucocyte count (> 15,000/mm³) at onset of the initial CDI episode was not predictive of recurrent CDI, which is contrary to results of Rodrigues-Pardi et al. [16]. These authors suggest that the patients with high leucocyte count had the more severe initial CDI episode which may leave the bowel more vulnerable to subsequent CDI. In our study, hypoalbuminemia had a statistically significant effect on the occurrence of CDI relapse. In the patients with the albumin level of < 25 g/L, the relapse developed in 70.27% vs 41.94% of patients with the stable clinical response ($p = 0.034$). Similar to our results, Rotramel et al. [17] and Shakov et al. [18] also proved a statistically significant effect of hypoalbuminemia on the occurrence of CDI relapse. 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, 19].

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 [20] research also demonstrated that the concomitant use of non-CDI antibiotics significantly affects the occurrence of CDI relapse ($p = 0.0012$). The authors of other studies came to the same conclusion [21–23]. The antimicrobial therapy for the concomitant infections may result in altering bowel microflora, favoring CD growth. More frequent occurrence of relapses due to the concomitant use of antibiotics for conditions not related to CDI was due to higher level of additional continuous disruption of the intestinal flora, which allows persistence of CD [3, 24]. In our study, a statistically significant effect of the use of proton pump inhibitors on the occurrence of CDI relapse was not observed. Studies published by the Lupşe et al. [6] and Rodrigues-Pardo et al. [16] demonstrated a statistically significant effect of proton pump inhibitors on the occurrence of CDI relapse, while Rotramel et al. [17] did not find that connection. Whether the gastric acid suppression is truly an independent RF for recurrent CDI remains unknown.

The results of our study showed that vancomycin was more effective than metronidazole in the elimination of CD toxins from the intestinal tract. After the completion of the CDI therapy, the persistence of CD toxins was found in 22.32% of patients treated with metronidazole compared to 9.09% of patients who were given vancomycin ($p = 0.003$). Similarly to our results, McFarland et al. [25] found that vancomycin was significantly more efficient than metronidazole in the elimination of CD toxins from the colon. In this study, 11% of patients treated with vancomycin *vs* 41.2% of patients given metronidazole ($p = 0.0004$) were positive for CD toxins in the stool after the completion of therapy. Wullt and Odenholt [26] registered the persistence of CD toxins after the treatment with metronidazole in 23% of patients, and the study of de Lalla et al. [27] showed that after the treatment with vancomycin, the persistence of CD toxins was found in 25% of patients. The literature data indicate that the post-therapy bacterial persistence is not conditioned only by the 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 the toxin production and the state of the immune system, that is, the production toxin-neutralizing Ig A antibodies [28, 29].

Previous studies showed greater efficacy of vancomycin compared to metronidazole in the elimination of CD toxins from the colon, but the studies did not prove the higher frequency of relapse in patients with the persistence of CD toxins [25, 29]. McFarland et al. [25] showed that after metronidazole treatment, the patients who had recurrences did not have a significantly higher frequency of the CD persistence (53.5%) than those who did not have the relapse (31.6%) [26]. Noren et al. [28] analyzed the link between microbial efficiency and clinical outcomes after the CDI therapy with metronidazole and concluded that in the case of persistence of CD toxins, the stable clinical response is achieved in 57% of patients *vs* 74% of patients with the stable clinical response. In accordance with the previous research, the results of our study also showed that the presence of CD toxins in the stool after the completion of the CDI therapy, did not affect significantly the occurrence of relapse. In our study, the persistence of CD toxins was registered in 13.87% of patients with the stable clinical response versus 23.94% of patients with the relapse ($p > 0.05$). After the treatment with metronidazole, this ratio was 19.01% *vs* 31.71% ($p = 0.08$), and after the treatment with vancomycin it was 9.82% *vs* 13.33% ($p = 0.16$). This finding could be interpreted by the previously proven fact that asymptomatic carriers, after the successful completion of the initial episode of CDI, developed a sufficient level of toxin-neutralizing A antibodies to CD, by which this population of patients acquire low risk of the CDI relapse. Therefore, in daily practice, after the successfully completed treatment, it is not recommended the routine testing of stool samples on the presence of CD toxins as a "control test of treatment success" [29].

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

Conclusion

Our data suggest that important RF for the 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 the CDI relapse should emphasize those group of patients.

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