British Journal of Healthcare and Medical Research - Vol. 12, No. 01
Publication Date: February 25, 2025
DOI:10.14738/bjhr.1201.18257.
Tugushev, A. S., & Cherkovska, O. S. (2025). Comparative Assessment of Hemostasis Patients with Compensated and Decompensated Cirrhosis. British Journal of Healthcare and Medical Research, Vol - 12(01). 224-234.

Comparative Assessment of Hemostasis Patients with Compensated and Decompensated Cirrhosis

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ABSTRACT

We have studied the pro- and anticoagulant systems in patients with compensated and complicated course of the disease in dynamics. The presence of thrombophilia in patients with compensated course of liver cirrhosis, which may be one of the pathogenetic factors in the development of complications, and disseminated intravascular coagulation in patients with decompensated cirrhosis, which is a consequence of thrombophilia and the cause of hemorrhagic syndrome, has been shown. The aim: to give the comparative assessment of the state of hemostasis system in patients with liver cirrhosis with uncomplicated and complicated course of the disease. Materials and methods: The study involved 240 patients with liver cirrhosis hospitalized during 2017-2021. 190 patients were assigned to the group with complicated - decompensated course of cirrhosis: 123 had gastrointestinal bleeding, 67 had ascites. 62 patients died during the follow-up. 50 patients were referred to the group of patients with uncomplicated - compensated course of the disease. At the time of examination they had no specific complaints. Assessment of procoagulant link included the determination of the number of platelets, prothrombin index, activated partial thromboplastin time, fibrinogen, and activity of coagulation factor F VIII. Assessment of anticoagulant link included the determination of protein C activity. Additionally, markers of thrombosis were assessed by the level of fibrinogen "B" and D-dimer. Results: When assessing the hemostatic system in decompensated patients with liver cirrhosis, the indicators of the pro- and anticoagulant link at admission and in dynamics were changed within wide limits, both in the direction of hypo- and hypercoagulation, regardless of the complications nature. In compensated patients, the standard coagulogram did not differ from normal values. At the same time, the activity of coagulation factor FVIII in 65.2% of patients was at the upper limit of the parameters taken as the norm, and in 35.6% it exceeded the upper limit of the norm. The activity of anticoagulant protein C in plasma in 88.0% of patients with LC was 1.5 - 1.8 times lower than the lower limit taken as the norm. At the same time, a decrease in the number of platelets, prothrombin index, fibrinogen, and an increase in the APTT level characteristic of decompensated patients can be regarded as manifestation of disseminated intravascular coagulation syndrome. Confirmation of the presence of disseminated intravascular coagulation syndrome is an increase in the level of D-dimer in blood, which was observed in 75.0% -97.0% of patients upon admission, and in 90.0% -99.0% in dynamics among the deceased, regardless of the complications nature. Conclusions: In compensated patients with liver cirrhosis, the state of hemostasis during the natural course of the disease is characterized by

imbalance in the direction of hypercoagulation, which is confirmed by a decrease in the activity of protein C against the background of normal or increased activity of the coagulation factor FVIII. Decompensated patients have DIC syndrome in varying degrees of severity, characterized by laboratory thrombocytopenia, a decrease in the prothrombin index, fibrinogen, an increase in APTT, the appearance of fibrin degradation products (D-dimer), which clinically determines the hemorrhagic syndrome in liver cirrhosis. Among the deceased patients, the content of D-dimer practically did not change over time, being increased in 90.0% of patients with bleeding and 99.0% with ascites.

Keywords: liver cirrhosis, hemostatic system, coagulopathy, thrombosis, bleeding, protein C, factor F VIII, disseminated intravascular coagulation syndrome.

INTRODUCTION

Based on the results of the consensus conference "Portal hypertension and variceal bleeding - unresolved problems" (Atlanta, June 4-6, 2007), it is customary to distinguish two main stages of liver cirrhosis: compensated and decompensated, characterized by the absence or presence of complications (ascites, bleeding from varicose veins, liver failure, jaundice). The stages differ in clinical course, treatment results, and mortality rates - pre- and postoperative. Compensated and decompensated cirrhosis should be considered two separate syndromes both in clinical practice and in clinical research [1-4].

The nature of violations of the hemostatic system in liver cirrhosis (LC) is complex, often unpredictable and concerns all its links - vascular-platelet, coagulation and fibrinolysis. It is accompanied by an imbalance of the pro- and anticoagulant systems, which is based on imbalance in the synthesis of both pro and anticoagulants in the liver - витамин К dependent factors [5-9]. It is generally accepted that with LC there is a state of hypocoagulation with an increased tendency to bleeding. However, a number of publications do not support this opinion, and the interpretation of laboratory parameters is explained by the standard methodology, where the anticoagulant and antifibrinolytic systems of hemostasis are insufficiently studied [1, 6-8]. Many researchers have established a state of hypercoagulability in LC, leading to intra- and extrahepatic thrombosis. The cause of bleeding, primarily from varicose veins of the esophagus and stomach, is not hypocoagulation as such, but rupture of varices due to hemodynamic disturbances and increased portal pressure [1, 2, 9-14]. Thus, with LC, both bleeding and thrombosis are possible.

When assessing the hemostatic system, it is necessary to determine both pro and anticoagulant components. And hypercoagulation can be interpreted as a primary defect only when the indicators of the anticoagulant system are within the normal range, and vice versa [1, 4, 9, 15-17]. In 2020, supplements were published in the American Association for the Study of Liver Diseases Practice Guidelines on vascular liver disease, thrombosis and bleeding in patients with liver disease, which critically reviewed the currently generally accepted data on the pathophysiological and clinical features of hemostasis disorders in patients with cirrhosis. which suggests further research in this direction [1, 6].

Thus, in view of the emerging doubts about nature of hemostasis system disorders in liver cirrhosis, it is urgent to study the pro- and anticoagulant systems of hemostasis in patients with liver cirrhosis, both during decompensation, when coagulopathy can be a consequence of

URL: http://dx.doi.org/10.14738/bjhr.1201.18257.

complications, and in compensated patients, when coagulopathy can be the cause of the development complications.

The Aim

To assess the state of the hemostasis system in patients with liver cirrhosis with an uncomplicated and complicated course of the disease.

MATERIALS AND METHODS

Subjects

A comparative assessment of the state of the pro- and anticoagulation hemostatic system in patients with cirrhosis with compensated and decompensated course of the disease was carried out.

Study Design and Settings

This prospective randomized controlled trial was conducted during 2017-2021 on the basis of the surgical departments of the city center of extreme medicine and emergency medical care, VitaCentre LTD and the 1st city hospital, therapeutic departments of the 1st and 4th city hospitals, the regional Zaporizhzhia hepatological center. The study was carried out in accordance with the basic bioethical standards of the Declaration of the World Medical Association of Helsinki on the ethical principles of scientific and medical research, with the patients' informed consent.

The study involved 240 patients with liver cirrhosis. Men - 154 (64.2%), women - 100 (35.8%). The patients' age ranged from 24 to 72 years. Viral etiology occurred in 78 patients (32.4%), alcoholic etiology in 93 (38.6%), a combination of virus and alcohol in 48 (20.1%), and a history of drug-induced hepatitis, drug addiction, Budd-Chiari syndrome, autoimmune hepatitis.

We compared groups of patients with a complicated - decompensated and uncomplicated - compensated course of the disease. Separately, the subgroups of decompensated patients were compared where treatment was effective and patients were discharged from the hospital, and where death was observed.

190 patients were included in the group with complicated LC. 123 had gastrointestinal bleeding (GI) from varicose veins of the esophagus (stomach), of which 49 (40.0%) patients were admitted with GI bleeding recurrence. 80 (65.0%) patients were discharged, 43 (35.0%) died. 67 patients had diuretic-resistant ascites, of which 26 (38.0%) patients were re-admitted. 48 (72.0%) patients were discharged, 19 (28.0%) died. The main cause of death in everybody was liver failure.

Basic therapy included the administration of terlipressin, albumin, vikasol, ursodeoxycholic acid preparations, lactulose, and probiotics. For resistant ascites, laparocentesis was performed. For bleeding from esophageal varices, tamponade with a Sengstaken–Blakemore probe was used. In case of recurrent bleeding, stenting of the esophagus with a self-expanding esophageal stent, endoscopic alloying of varixes.

50 patients were assigned to the group with an uncomplicated course of the disease. 40 (80.0%) had a history of GI bleeding, 5 (10.0%) had edematous-ascites syndrome. Five (10.0%) patients

were diagnosed for the first time after a planned visit to the hepatological center. At the time of the control examination, they had no specific complaints. The functional parameters of the liver of everybody were within the normal range (Child-Pugh class A). There was no statistical difference in age, sex, comorbidity between the groups. The state of the pro- and anticoagulant system was purposefully examined in all patients.

Study Procedures

Evaluation of the procoagulant link included the determination of the number of platelets (normal - 180-320x109 / l), prothrombin index (80-120%), activated partial thromboplastin time (35-50´´), fibrinogen (2.2-4.4 g / l), activity of coagulation factor F YIII (50-200%). Assessment of the anticoagulant link included the determination of protein C activity (70-130%). Additionally, markers of thrombosis were assessed according to the level of fibrinogen "B" (normally absent) and D-dimer (norm - up to 500.0 ngFEU/ml). Control studies in decompensated patients were carried out every 3-4 days - over time, in compensated patients - during control examinations.

Statistical Analysis

Statistical processing of research results and construction of a mathematical model of the processes was carried out by the methods of variation statistics, implemented by the standard statistical analysis software packages "STATISTICA® for Windows 6.0" (StatSoft Inc., No. AXXR712D833214FAN5). The mean (M), the standard deviation (σ), the standard error of the representativeness of the mean (m) were calculated, and the 95% confidence interval of the mean was calculated. The results are presented as M ± m, the level of $p < 0.05$ was taken as statistically significant. To assess the relationship between the signs, correlation analysis was used with the calculation of Spearman's rank correlation (R).

RESULTS

Assessment of the Hemostasis System in Patients with Complicated LC

Procoagulant Hemostasis:

Platelets:

In the group of patients admitted with complications of cirrhosis, and where therapy was effective (discharged), in 55.2% of patients with gastrointestinal bleeding and 88.2% with ascites, the platelet count at admission was more than $100x10^9$/L. In dynamics, similar indicators were observed in 81.2% and 88.2% of patients, respectively. And, conversely, in this group, the number of patients where the platelet level was less than $60x10^9$/L decreased - 10.4% of patients with bleeding and 5.9% of patients with ascites upon admission to the hospital, 9.1% and 0%, respectively, at discharge ($p < 0.05$) (Table).

Among the deceased patients, normal platelet counts on admission were in 73.3% of patients with GI bleed and in 61.5% of patients with ascites. Less than 60x109 / l - in 6.7% and 15.4%, respectively. That is, we cannot talk about the initial role of thrombocytopenia, and, accordingly, an increased tendency to bleeding as a prognostic factor for the development of complications. In control studies, the number of patients with moderate and severe thrombocytopenia, in contrast to surviving patients, increased, and more among patients with ascites. That is, a decrease in the number of platelets over time has a certain prognostic significance.

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Prothrombin Index (PI):

In the group of discharged patients, in 54.0% of patients with gastrointestinal bleeding and 26.9% with ascites, PI at admission was more than 80 g/l. In dynamics, similar indicators were observed in 76.3% and 48.9% of patients. Accordingly, the number of patients decreased, where PI was in the range of 60-80 g l and less than 60 g/l ($p < 0.05$).

Among the deceased patients, normal PI values at admission were in 35.7% of patients with GI bleeding and in 60.0% - with ascites. In control studies, this ratio practically did not change, as well as the percentage of patients with PI values in the range of 60-80 g/l and less than 60 g/l. That is, the normalization of the prothrombin index in dynamics has a definitely positive prognostic value.

Fibrinogen:

In the group of discharged patients, in 66.0% of patients with GI bleeding and 73.1% with ascites, fibrinogen at admission was more than 2.2 g / L. In dynamics, the percentage of patients with normal fibrinogen levels increased to 78.8% and 94.7%, respectively ($p < 0.05$).

Among the deceased patients, normal fibrinogen levels at admission were similar to those in those discharged. In control studies, there were certain differences in patients with GI bleeding and ascites. With bleeding, the number of patients with normal fibrinogen values practically did not change, while in patients with ascites the number of patients with low fibrinogen values increased almost threefold - from 8.8% to 22.2% ($p < 0.05$).

Table: Indicators of the hemostasis system in patients with ascites and gastrointestinal bleeding from esophageal varices at admission and in dynamics, depending on the outcome of treatment

Indicators	Number of patients (190)							
	GI bleeding (123)				Ascites (67)			
	Discharged (74)		Died (49)		Discharged (48)		Died (19)	
	At Admission, %	In Dynamics, %	At Admission, %	In Dynamics, %	At Admission, %	In Dynamics, %	At Admission, %	In Dynamics, %
Plateles:								
> 100	55,2*	81,2*	73,3	70,0	88,2	88,2	61,5*	40,0*
60-80	34,5*	9,1*	20,0	20,0	5,9	11,8	23,1*	40,0*
< 60	10,4	9,1	6,7	10,0	5,9	0	15,4	20,0
PI:								
> 80	54,0*	76,3*	35,7	33,6	26,9*	48,9*	60,0	61,3
60-80	40,0	23,7	57,3	59,6	61,6	48,9	30,0	26,7
< 60	6,0	0	7,0	6,8	11,5	2,2	10,0	12,0
Fibrinogen:								
> 2,2	66,0*	78,8*	65,4	68,0	73,1*	94,7*	91,2	77,8
< 2,2	34,0*	21,2*	34,6	32,0	26,9*	5,3*	8,8*	22,2*
APTT:								
< 35	7,2	0	0	0	11,1	50,0	20,0	20,0

35-50	42,8	50,0	42,1	25,0	66,7	50,0	20,0	60,0
> 50	50,0	50,0	57,9	75,0	22,2	0	60,0	20,0
Protein C:								
< 70	71,5*	68,0*	80,0*	75,0*	71,4*	90,0*	88,0*	94,0*
> 70	28,5*	32,0*	20,0*	25,0*	28,6*	10,0*	12,0*	6,0*
F VIII:								
> 150	71,5*	88,0*	60,0	85,8*	66,7*	72,6*	92,0*	94,0*
< 150	28,5*	12,0*	40,0	14,2*	33,3*	27,4*	8,0*	6,0*
Fibrinogen «B»:								
< ++	39,0*	70,0*	79,2*	50,0*	58,3*	66,7*	90,0*	85,4*
+++ - ++++	61,0*	30,0*	20,8*	50,0*	41,7*	33,3*	10,0*	14,6*
D-dimer:								
> 500	79,0*	56,3*	75,0*	90,0*	85,7*	52,0*	97,0*	99,0*
< 500	21,0*	43,7*	25,0*	10,0*	14,3*	48,0*	3,0*	1,0*

* - difference between groups of survivors and deaths, p <0.05

Partially Activated Thrombin Time **(APTT):**

More than half of the patients admitted with complications of liver cirrhosis showed a change in the indicators of partially activated thrombin time, both in the direction of decreasing and decline. Moreover, in dynamics, if among discharged patients, APTT tends to normalize, then among deceased patients with GI bleeding it lengthens (a sign of hypocoagulation), and among deceased patients with ascites, on the contrary, decreases (a sign of hypercoagulation), which does not allow taking into account APTT indicators, as prognostic factor.

Coagulation Factor F VIII**:**

In 71.5% of discharged patients with GI bleeding and 60.0% of those who died, the activity of procoagulant coagulation factor F VIII exceeded normal values (70-150%). In those admitted with ascites, increased activity of F VIII was in 66.7% of those discharged and in 92.0% of patients who subsequently died. It is characteristic that in dynamics the percentage of patients with increased F VIII activity in all groups increased, reaching 85.8% -94.0% (p <0.05), which is not entirely consistent with the data on the role of hypocoagulation in patients with LC.

Anticoagulant Hemostasis:

Protein C:

It is characteristic that, in contrast to coagulation factor F VIII, the activity of the anticoagulant factor protein C in 71.4% -88.0% of patients hospitalized with complications of cirrhosis was reduced, amounting to less than 70% (p <0.05). The low activity of protein C remained the same in dynamics, both in discharged and deceased patients, in 68.0% and 75.0%, respectively, with GI bleeding, and 90.0% -94.0% - with ascites, which is also does not agree with the prevailing role of hypocoagulation in patients with LC (p <0.05).

Thrombosis Markers:

Fibrinogen B**:**

In the group of discharged patients in 61.0% of patients with GI bleeding and 41.7% with ascites, the level of fibrinogen "B" at admission was 3-4 plus points. In dynamics, the percentage of patients with a high content of fibrinogen "B" decreased to 30.0% and 33.3%, respectively. And, conversely, the number of patients where fibrinogen "B" was absent increased, from

URL: http://dx.doi.org/10.14738/bjhr.1201.18257.

39.0% at admission to 70.0% at discharge with GI bleeding and from 58.3% to 66.7%, respectively, with ascites ($p < 0.05$).

Among the deceased patients, on the contrary, there is an increase in the number of patients with an increased level of serum fibrinogen "B" in dynamics and in patients with GI bleeding and ascites - from 20.8% to 50.0% and from 10.0% to 14.6 %, respectively ($p < 0.05$).

***D-dimer*:**
The dynamics of the content of D-dimer in the blood is similar to the dynamics of changes in fibrinogen "B". At admission, a D-dimer level of more than 500.0 ng FEU/ml was observed in 75.0% -97.0% of hospitalized patients with both bleeding and ascites. In dynamics, the percentage of patients with a high content of D-dimer in the discharged group decreased from 79.0% to 56.3% in the case of GI bleeding, and from 85.7% to 52.0% in the case of ascites. And in the group of the deceased, on the contrary, it increased - from 75.0% to 90.0% with GI bleeding, and from 97.0% to 99.0% with ascites ($p < 0.05$).

Assessment of the Hemostasis System in Patients with Uncomplicated LC:
Procoagulant Hemostasis:
In all patients with LC with an uncomplicated course, the prothrombin index, fibrinogen and APTT values did not differ from normal values.

The platelet level in 37 (74.0%) patients was above $100x10^9$/ l, in 10 (20.0%) - within 60-$80x10^9$/l, and only in 3 (6.0%) - below $60x10^9$/l ($p < 0.05$).

The activity of coagulation factor FVIII in 32 (65.2%) patients was at the upper limit of the parameters taken as the norm (150%), and in 18 (35.6%) - it exceeded the upper limit of the norm (more than 150%) ($p < 0.05$).

Anticoagulant Hemostasis:
The activity of anticoagulant protein C in plasma in 44 (88.0%) patients with uncomplicated LC was 1.5 - 1.8 times lower than the lower limit accepted as the norm - 70%, on average 40.0-50.0%, and only in 6 (12.0%) was in normal ranges ($p < 0.05$). The low activity of protein C remained the same in dynamics, both in discharged and deceased patients, in 68.0% and 75.0%, respectively, with GI bleeding, and 90.0% -94.0% - with ascites, which is also does not agree with the prevailing role of hypocoagulation in patients with LC ($p < 0.05$).

Thrombosis Markers:
In 6 (12.0%) patients, the presence of fibrinogen "B" ++ in the plasma was noted. In 4 (8.0%), there was an increase in the level of D-dimer above 500.0 ng FEU /ml ($p < 0.05$).

DISCUSSION

When assessing the hemostasis system in decompensated patients admitted to the hospital with complications of cirrhosis, regardless of whether bleeding or ascites, the indicators of the pro- and anticoagulant link on admission and in during observation changed over a wide range, both towards hypo- (decrease in platelets, prothrombin index , increased APTT) and hypercoagulation (presence of fibrinogen "B", decreased APTT, protein C activity, increased clotting activity F VIII), which can be interpreted in different ways. These data coincide with

the opinion of various authors, which also indicate that with LC, both hypercoagulation with an outcome in thrombosis and hypocoagulation with hemorrhagic complications are possible, that is associated with the presence of hemostatic imbalance. The reason for this imbalance is that in the liver the synthesis of all proteins of the coagulation system occurs as procoagulants (with the exception of von Willebrand factor and factor VIII) - vitamin K-dependent factors II, V, VII, IX, X, XI, XII, fibrinogen and fibrin-stabilizing factor XIII and coagulation inhibitors (antithrombin III, proteins C, S, a2-macroglobulin, α-antitrypsin, metalloprotease ADAMTS-13, etc.). Proteins C and S are also vitamin K-dependent. Procoagulants also include thrombopoietin, a cytokine that regulates the maturation of megakaryocytes and the formation of platelets in the bone marrow. With cirrhosis, the amount of these proteins decreases in varying proportions, which leads to an imbalance in the hemostatic balance in one direction or another and, accordingly, to the patient's predisposition to bleeding or thrombosis.

At the same time, there are different points of view, whether the hemostatic imbalance is one of the causes of LC complications or their consequence [13, 20-24].

To answer this question, we conducted studies of the hemostasis system in patients with liver cirrhosis in the stage of compensation - during control examinations, which, in our opinion, reflects hemostasis during the natural course of the disease.

It was noted that the standard indicators of the procoagulant link of the hemostasis system (PI, APTT, fibrinogen) did not differ from normal indicators. At the same time, the activity of procoagulant factor F VIII in 65.2% of patients was at the upper limit of the norm, and in 35.6% it exceeded normal values. In contrast to the procoagulant link, the activity of anticoagulant protein C in plasma in 88.0% of patients with uncomplicated LC was 1.5 - 1.8 times lower than the lower limit taken as the norm. These data can serve as confirmation of the state of thrombophilia in patients with LC with its natural course. At the same time, a decrease in the number of platelets, indicators of the prothrombin index, fibrinogen, and an increase in the APTT level in hospitalized patients with complications of cirrhosis can be regarded as a manifestation of varying degrees of severity of disseminated intravascular coagulation syndrome (DIC), manifested by consumption coagulopathy. Confirmation of the presence of disseminated intravascular coagulation syndrome is the presence of fibrin degradation products - fibrinogen "B" and D-dimer in the blood of most patients with LC complications. The D-dimer level was increased in 75.0% -97.0% of hospitalized patients with both bleeding and ascites. Moreover, a positive outcome correlated with a decrease in the D-dimer content over time. Among the deceased patients, the content of D-dimer practically did not change, being increased in 90.0% of patients with GI bleed and 99.0% with ascite. The issue of disseminated intravascular coagulation in patients with LC remains a subject of discussion. At the same time, the majority of authors support the opinion that mild DIC is involved in the pathogenesis of coagulopathy in some patients with diffuse liver diseases, and with CP there is a greater risk of developing an advanced DIC.

Observation of 4 patients with uncomplicated LC is indicative. 2-2.5 weeks after the study of the coagulogram, where there were signs of hypercoagulation (an increase in the activity of the procoagulant F VIII and a decrease in the activity of the anticoagulant protein C), they were admitted to the surgical department with a clinic of gastrointestinal bleeding. During control laboratory examinations, everybody had a decrease in the number of platelets, PI, fibrinogen,

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lengthening of APTT – signs of hypocoagulation, the appearance of fibrinogen 'B' and a multiple increase in the content of D-dimer – signs of thrombosis or disseminated intravascular coagulation.

CONCLUSIONS

1. Changes in hemostasis that accompany liver pathology affect all levels of the coagulation system, leading to a hemostatic imbalance. In this case, a comparative assessment of both the pro and anticoagulant links of the hemostasis system is required.
2. The state of hemostasis with the compensated course of liver cirrhosis is characterized by imbalance towards hypercoagulation, as evidenced by a decrease in the activity of the anticoagulant factor protein C against the background of normal or increased activity of the procoagulant coagulation factor FVIII, which occurs, on average, in 90% of patients with an uncomplicated course of the disease.
3. The state of hemostasis with decompensation of liver cirrhosis is characterized by the presence of varying degrees of severity of DIC syndrome, laboratory confirmation of which is thrombocytopenia, a decrease in the prothrombin index, fibrinogen, an increase in APTT, the appearance of fibrin degradation products (fibrinogen 'B', D-dimer), that occurs in patients with a complicated course of the disease. Among the deceased patients, the content of D-dimer practically wasn't changable over time, being increased in 90.0% of patients with bleeding and 99.0% of patients with ascites.

Prospects for Further Research:

It is necessary to further research the pro- and anticoagulant systems of hemostasis in patients with liver cirrhosis, both during decompensation, when coagulopathy can be a consequence of complications, and in compensated patients, when coagulopathy can be the cause of complications in order to determine objective criteria of hemostatic imbalance and its effective correction.

Conflicts of Interest: authors have no conflict of interest to declare.

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