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# ROLE OF SURFACTANT PROTEIN SP-D IN THE DIAGNOSIS OF PULMONARY COMPLICATIONS IN PATIENTS WITH COMBINED THORACIC INJURY

## O. Boiko, Yu. Volkova

**The aim:** to evaluate the informativeness of the content of SP-D in the blood of patients with combined thoracic trauma as a marker of the severity of traumatic illness and the impact of the proposed modifications of the intensive care algorithm on treatment outcomes.

**Material and methods.** The basis of this study is a statistical analysis of the results of a comprehensive examination of 92 patients with thoracic trauma. Control points were 1st, 3rd, 7th and 12th day of treatment. The severity of the injury was determined according to the ISS scale, the condition of patients at the time of admission according to the ARASNE II scale, the level of SP-D in the blood, the degree of pulmonary hypertension, the number of bed-days in the intensive care unit (IC). 3 groups of patients were identified. Group I - standard IC protocol, group II – standard IC protocol with the addition of ceruloplasmin, group III – standard IC protocol with the addition of a solution of D-fructose-1,6-diphosphate sodium salt of hydrate. Parametric statistics methods were used to process the obtained data.

**Results.** In patients of group I, the maximum numbers of SP-D in the blood were determined, which had a positive strong correlation during the entire observation period with the frequency of pulmonary complications and the duration of treatment in the IC department. In group II, the administration of ceruloplasmin neutralized the negative effect of oxidative stress on the surfactant, so the average SP-D in the blood only on the 3rd day exceeded the reference values by 20 %, which affected the lack of correlations between pulmonary parenchyma and duration of treatment. In group III, the addition of a solution of D-fructose-1,6-diphosphate sodium salt hydrate had a positive effect on the general condition of patients as a whole, but throughout the study period SP-D figures in the blood exceeded the starting and reference, which affected the presence of strong and medium positive correlation between them, the degree of pulmonary hypertension and the length of stay in the IC department.

**Conclusions.** In patients with combined thoracic trauma, it is important when planning patient management tactics to diagnose the content of surfactant protein SP-D in the blood during the entire period of stay in the intensive care unit. The level of SP-D in the blood of patients with combined thoracic trauma is a highly informative diagnostic marker of the functional state of the lung parenchyma (surfactant). An increase in its numbers three times indicates the beginning of the development of acute lung injury syndrome (exudative phase). Reduction of its figures in the course of respiratory distress syndrome by half the values in the exudative phase indicates the beginning of the proliferative phase and improvement of patients. The leading mechanism for the development of acute lung injury syndrome in patients with combined thoracic trauma. There is oxidative stress, so the appointment of ceruloplasmin as an adjunct to the standard protocol of intensive care is pathogenetically justified

**Keywords:** combined thoracic trauma, surfactant, SP-D, pulmonary hypertension, respiratory function, complications, duration of treatment, intensive care, ceruloplasmin

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# 1. Introduction

A featur e of injuries in recent decades is the increase in the severity of injuries and changes in their structure [1, 2]. The proportion of polytrauma (MT) has significantly increased, reaching 5.5–35 % according to various a uthors [3, 4]. The structure of polytrauma is very variable and depends on many factors. According to summary statistics, it is represented by the following localization of the dominant injuries: traumatic brain injury – 16.5–28.7 %, thoracic trauma – 18–55.0 %, abdominal trauma – 22.1–30.0 %, pelvis – 14.2–26, 0 %, spine – 5–7.0 %, limbs – 42–87.0 % of observations [5, 6]. The disturbances of vital functions and parameters of homeostasis caused by a thoracic trauma at a polytrauma have a specific pathogenesis and certain clinical forms [7, 8].

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Thoracic trauma, represented morphologically by a set of lesions, is a special form of severe polytrauma, which develops due to the mutual influence of increasing pathological processes and the formation of new links in the pathogenesis [9, 10].

At damage of any localization there are disturbances of anatomic integrity of fabrics or bodies [11, 12], entailing frustration of their function that is especially appreciable at big damages of soft tissues, bone structures and internals of a thorax [13, 14]. The most typical manifestations are central nervous system dysfunction, acute blood loss, endotoxicosis and acute respiratory failure (ARF), which is associated not so much with direct chest damage as with the development of parenchymal lung failure in severe injuries of another location [13]. In these cases, ARF is one of the leading links in the chain of pathological processes [14].

In particular, the nonspecific nature of pulmonary insufficiency under many extreme conditions has been studied and described by D. G. Ashbaug et al. (1967) as a syndrome of "shock lung", a syndrome of acute pulmonary injury, acute respiratory distress syndrome in adults [11, 15], the main pathogenetic mechanism of which is the impact on the alveoli of toxic products and microembolizat ion of pulmonary capillaries [16, 17]. This leads to impaired diffusion of gases through the alveolar membrane, and as a result – to respiratory failure [18, 19]. These phenomena are joined by a decrease in activity and production of surfactant, which leads to the decline of alveoli and the formation of microatelectases [20, 21].

The interaction of these powerful factors leads to significant metabolic disorders [22] and serves as a logical explanation for the high mortality and frequency of complications of thoracic trauma in polytrauma in the posttraumatic period [23, 24].

It should be noted that the complicated course of thoracic trauma in MT occurs in 36.8–75.5 % of cases [22]. In this case, the main factors contributing to the development of complications are blood loss with a deficit of circulating blood volume of more than 40 %, severe damage to the chest, accompanied by aspiration-regurgitation syndrome, cardiovascular dysfunction, and prolonged ventilation [25, 26]. Therefore, an important point during the entire period of intensive care is the assessment of the dynamics of the respiratory capacity of the body, which determine the results of treatment of patients with thoracic trauma with polytrauma and the prognosis in general.

Given that multimarker panels are used at the current level to identify and predict the manifestations of acute lung injury syndrome, it is important to find their undefined components, especially in patients with combined thoracic trauma [31, 32]. According to the electronic databases MEDLINE and EMBASE for the last 10 years, no information was found on the role of surfactant protein SP-D in this category of patients, which justified the purpose of this study.

The aim of the study was to evaluate the informativeness of SP-D content in the blood of patients with combined thoracic trauma as a marker of the severity of traumatic illness and the impact of the proposed modifications of the intensive care algorithm on treatment outcomes.

#### 2. Material and methods

This study is based on a statistical analysis of the results of a comprehensive examination of 92 patients with thoracic trauma who were treated in the polytrauma department of the Municipal Non-Profit Enterprise "Clinical Hospital of Ambulance and Emergency Care named after prof. O. I. Meshchaninov" Kharkiv City Council in the period 2017–2019. Ethical aspects of the work were approved at the meeting of the Commission on Biomedical Ethics of the Kharkiv National Medical University of the Ministry of Health of Ukraine (Protocol No. 9 of 21.09.2017). All patients signed an informed consent to participate in the study.

The effectiveness of the proposed methods of treatment in the process of cohort clinical open prospective study in the division of patients into 3 stratified groups was eval u ated. Randomization was performed by the method of "envelopes".

Group I included 30 patients with combined thoracic trauma, who received intensive care (IC) of the received injuries according to the unified clinical protocol of emergency medical care of the Ministry of Health of Ukraine "Polytrauma" (2016).

Group II included 30 patients with combined thoracic trauma, who in addition to the main IC protocol was prescribed a solution of ceruloplasmin in a daily dose of 6 mg/kg diluted in 200 ml of 0.9 % sodium chloride solution at a rate of 30 drops per minute intravenously during the first week hospital stay.

Group III included 32 patients with combined thoracic trauma, who in addition to the main IC protocol was prescribed a solution of D-fructose-1,6-diphosphate sodium salt hydrate intravenously in a dosage of 150 mg/kg of ideal body weight 2 times a day (after 12 hours) at a rate of 10 ml per minute during the first 7 days of treatment.

Verification of the diagnosis of thoracic trauma and its dynamics was established on the basis of clinical and anamnestic features, radiographic data, determination of blood gas composition. The severity of injuries of the anatomical areas was determined using the ISS scale (Injury Severity Score), the degree of pulmonary damage in the dynamics was assessed by the LIS scale (Lung Injury Score), the determination of the ARF stage was performed according to the classification of V. L. Cassil (1997). In patients with intrapleural trauma, studies were performed after evacuation of the latter.

Criteria for inclusion in the study: age up to 60 years, the presence of lung damage in polytrauma, the possibility of productive contact with the patient at admission (14– 15 points for SCG), obtaining informed consent, no history of blood diseases, cancer, COPD, bronchial asthma, aggravated heredity, alcoholism, mental disorders, allergic reactions, blood transfusions, moderate severity of injuries (9–24 points on the ISS scale), the number of points on the ARACHE II scale at the time of admission no more than 10 points, lack of inotropic support in the prehospital stage.

Criteria for non-inclusion in the study: age over 60 years, the presence of damage to the craniofacial anatomical and functional area, as well as abdominal organs, musculos k eletal system on the scale of severity (AIS), which belonged to the category "trauma is critical, survival is unlikely", the presence of post-traumatic heart attack.

To analyze the dynamics of the traumatic disease in patients, control points were selected – 1st, 3rd, 7th and 12th day of hospital stay. This was due to the fact that, despite the absence of severe injuries – 9–24 points on the ISS scale, up to 10 points on the ARACHE II scale – the presence of combined injuries in the presence of thoracic trauma increases the likelihood of acute lung injury syndrome, the period of development of which in Blood for the study in patients was taken on an empty stomach at 8.00 am on the appropriate day. Determination of the level of SP-D (Pulmonary surfactant-associated protein D) in the serum of patients was performed by enzyme-linked immunosorbent assay on the analyzer "Labline-90" (Austria) using a commercial test system manufactured by "ELISA" (USA) according to the instructions included composition of the set. Reference values were 20–100 ng/ml.

The condition of the vessels of the small circle of blood circulation (the main pulmonary artery) was assessed using transthoracic echocardiography with Doppler. The maximum systolic pressure in the pulmonary artery was determined in a continuous-wave Doppler mode. The calculation of the value of systolic pressure in the pulmonary artery was performed on the velocity of the tricuspid regurgitation jet using a modified Bernoulli equation [34]. The pressure in the right atrium was assessed by a method based on determining the diameter of the inferior vena cava and its response to deep breathing. The presence of pulmonary hypertension was determined at systolic pressure in the pulmonary artery more than 30 mm. To assess the severity of pulmonary hypertension (PH) used a classification based on the degree of increase in systolic pressure in the pulmonary artery (Table 1) [35].

Table 1

Classification	of pulmonary	hypertension

Degree	Pulmonary hypertension	Systolic pressure in the pulmonary artery, mmHg		
0	absence	<20		
1	moderate	30–50		
2	significant	50-80		
3	expressed	>80		

The dependence of PH severity and the number of bed-days in the IC department on the level of SP-D in the blood was determined against the background of the use of each of the treatment protocols.

Statisti c al data processing was performed on a personal computer. Verification of the significance of the obtained data, which were previously entered into Excel spreadsheets, was carried out using Student's t-test (for n<100) at a given level of reliability p=0.95, for the possibility the use of the Student's criterion introduced the Bonferoni amendment. Correlation analysis was used to determine the relationship between the individual parameters. Pearson's linear correlation coefficient was used to determine the relationship and closeness of this relationship between individual events. Linear correlation analysis allows you to establish the presence of direct relationships between variables in their absolute values. The formula for calculating the correlation ship between

the features is linear, the Pearson coefficient r accurately establishes the closeness of this relationship. At values of r 0.3-0.5, the relationship between events is relatively weak; at values of 0.5-0.7, the connection has a medium strength. If the value of r exceeds 0.7, the bond is strong, and if it exceeds 0.9, it is very strong [36].

## 3. Research results

Given the fact that, according to many researchers [37–39], SP-D is defined as a marker of lung damage and an indicator of inflammation control in them, and is a key regulator of functions and programming factor of the phenotype of alveolar macrophages – the main cells of the pulmonary immune system, it can be considered as a bivalent regulator of the pathological process, which is important in determining the functional state of the respiratory capacity of the body.

During the study, the mean serum SP-D content determined for each of the control points was compared with the baseline values of this indicator (Table 2), and a correlation analysis was performed between its level and the results of treatment of patients (Table 3).

Table 2 Dynamics of SP-D content in blood of patients of groups I. II and III

groups i, ii and iii							
SP-D level, ng/ml	Group I n=30	Group II n=30	Group III n=32				
1 day after injury	84.9±7.1	81.6±9.4	82.7±9.1				
3 days after injury	221.4±25.2 <sup>1,2</sup>	114.6±8.1 <sup>1,2,4</sup>	182.2±16.4 <sup>1,3,4</sup>				
7 days after injury	166.7±18.2 <sup>1,2,3</sup>	97.9±6.1 <sup>1,2,4</sup>	124.2±10.7 <sup>1,4</sup>				
12 days after injury	127.1±16.8 <sup>1,2</sup>	84.9±7.2 <sup>2</sup>	110.6±8.4 <sup>1,4</sup>				

Note:  ${}^{1}-p<0.05$  – probable difference in relation to the starting level;  ${}^{2}-p<0.05$  – probable differences between groups I and II;  ${}^{3}-p<0.05$  – probable differences between groups I and III;  ${}^{4}-p<0.05$  – probable differences between groups II and III

When per forming a statistical analysis of the dynamics of SP-D in the serum of all studied patients, the increase in its level was regarded as damage to the surfactant and the risk of developing acute lung injury syndrome. The redistribution of this marker in the body towards the bloodstream significantly reduces its amount in the lungs, so we can predict an increase in susceptibility to infections, which in traumatic disease in patients with combined thoracic trauma worsens the condition and prognosis.

Therefore, on the first day of stay in the separated IC in all patients the level of SP-D in the blood was within the reference values and was  $84.9\pm7.1$  ng/ml,  $81.6\pm$  $\pm9.4$  ng/ml and  $82.7\pm9.1$  ng/ml in groups I, II and III, respectively. On the 3rd day of treatment in group I, its concentration increased threefold and was  $221.4\pm$  $\pm25.2$  ng/ml, which was probably (p<0.05) higher than on the first day. In group II, the level of SP-D in the blood was  $114.6\pm8.1$  ng/ml, which probably (p<0.05) exceeded the starting figures and probably (p<0.05) was less than in patients of group I.

In group III, the concentration of SP-D in the blood was  $182.2\pm16.4$  ng/ml, which was 2 times more likely (p<0.05) than baseline and was likely (p<0.05) in 1.5 times higher than the level in group II.

The mean level of SP-D in the blood of patients in group I exceeded by 10 % its value in group III without a significant difference between them.

On the 7th day of IC in all studied patients there was a positive dynamics of this indicator. Thus, in group I, its level in the blood decreased by 20 % from the rate on the 3rd day, probably (p<0.05) 2 times higher than the starting values, probably (p<0.05) 2 times higher than the level in group II and was  $166.7\pm18.2$  ng/ml.

In group II on the 7th day of treatment, the level of SP-D in the blood of patients was  $97.9\pm6.1$  ng/ml, which had no significant differences from its baseline values. However, this was probable (p<0.05) compared with group I (166.7±18.2 ng/ml) and group III (124.2±10.7 ng/ml).

In group III on the 7th day of hospital stay the level of SP-D in the blood of patients was  $124.2\pm10.7$  ng/ml, which was probably (p<0.05) was greater than its values on the 1st day treatment. Also on the 7th day of intensive care, the concentration of SP-D in the blood of patients in group III probably (p<0.05) exceeded those in group II.

12 days after injury in group I patients receiving IC according to the standard protocol, the level of SP-D in the blood was  $127.1\pm16.8$  ng/ml, which probably (p<0.05) exceeded the initial values of this protein almost 2 times with the corresponding clinical picture of the course of traumatic illness.

In group II on the 12th day of hospital stay, this figure was completely restored and was  $84.9\pm7.2$  ng/ml, which was probably (p<0.05) 2 times less than its level in group I.

In group III, the content of SP-D in the blood of patients approached the initial values, was  $110.6 \pm \pm 8.4$  ng/ml, which was probably (p<0.05) less than its level in group I and probably (p<0.05) more than its level in group II.

When per forming a correlation analysis on the first day of IC in all groups of patients, despite the presence of lung contusion with fractures of the ribs, with or without intrapleural traumatic volumes, no stati s tically significant relationship was found between the level of SP-D in the blood of patients and pulmonary hypertension and the number of bed-days in the IC department. This indicates the low informativeness of this diagnostic marker of surfactant in the first 24 hours after patients with combined thoracic trauma. When it is included in the multi-marker diagnostic panel when a polytrauma is admitted to the hospital, the value of this indicator is only in the determination of anamnestic data (COPD, bronchial asthma, etc.).

On the 3rd day of treatment in patients of group I was found a very strong positive relationship SP-D – systol i c pressure in the pulmonary artery (r=0.91, p<0.05), which coincided with the development of more than 50 % patients of this group of the exudative phase of the syndrome of acute lung injury. Also in the victims of group I was found a strong positive relationship on the 3rd day of treatment with SP-D – systolic pressure in the pulmonary artery (r=0.91, p<0.05) and SP-D – t h e number of bed-days in IC department (r=0.91, p<0.05), which is due to the more severe course of their traumatic illness.

On the 7th day of stay in the hospital ligament SP-D – s y stolic pressure in the pulmonary artery (r=0.78, p<0.05) and SP-D – the number of bed-days in the IC department (r=0.86, p<0.05) were also significant, which determined a strong positive relationship and indic ated the further pathogenetic development of acute lung injury, when the exudative phase was transformed into a proliferative phase in most patients in this group.

Given the impact on the course of traumatic disease in general in victims of group I complications of combined thoracic trauma, and on the 12th day of hospital stay correlations SP-D – systolic pressure in the pulmonary artery (r=0.71, p<0.05) and SP-D – the number of bed-days in the IC department (r=0.74, p<0.05) were strongly positive.

Table 3

Correlation dependence (r) of the degree of pulmonary hypertension and the number of bed-days on the level of SP-D in the blood of the studied patients

Indicator	1 day	3 day	7 day	12 day				
Type of treatment – Standard IC protocol								
SP-D – Systolic pressure in the pulmonary artery	0.32	0.91*	0.78*	0.71*				
SP-D – Number of bed-days in the IC department	0.32	0.81*	0.86*	0.74*				
Type of treatment – Standard IC protocol + ceruloplasmin								
SP-D – Systolic pressure in the pulmonary artery	0.31	0.56	0.32	0.26				
SP-D – Number of bed-days in the IC department	0.29	0.59*	0.34	0.27				
Type of treatment – Standard IC protocol + solution D-F-1,6-BF								
SP-D – Systolic pressure in the pulmonary artery	0.32	0.76*	0.54	0.59*				
SP-D – Number of bed-days in the IC department	0.31	0.72*	0.52	0.71*				

*Note:*\*-p < 0.05 - correlations are plausible

In turn, in group II was statistically significant correlation of SP-D – the number of bed-days in the IC department (r=0.59, p<0.05) in the form of a mean positive relationship, only on the 3rd day of treatment. Subsequently, on the 7th day of observation, this relationship was positive and relatively weak, r=034, p<0.05 with its subsequent loss on the 12th day of IC.

The absence of statistically significant correlations in patients of group II indicates a direct effect of additional administration of ceruloplasmin on the surfactant in them, confirms its pathogenetic purpose and makes the mechanism of oxidative stress leading in determining the prognosis of traumatic disease in patients with combined thoracic trauma.

In group III, where patients additionally received a soluti on of D-fructose-1,6-diphosphate sodium salt hydrate, on the 3rd day of treatment between was found a strong positive relationship SP-D – systolic pressure in the pulmonary artery (r=0.76, p <0.05), which coincided with the development in less than 50 % of patients in this group of the exudative phase of the syndrome of acute lung injury. Group III victims also showed a strong positive SP-D relationship – the number of bed-days in the IC department (r=0.76, p<0.05) on the 3rd day of treatment.

On the 7th day of hospital stay, SP-D - pulmonary artery systolic pressure (r=0.54, p<0.05) and SP-D – number of bed-days in IC department (r=0.52, p<0.05) were average positive, indicating further pathogenetic development of acute lung injury, but in a less malignant form than in patients of group I, due to increased erythrocyte function as a leading pathogenetic mechanism of action of D-fructose-1,6-diphosphate solution of sodium hydrate.

On the 12th day of hospital stay, a strong positive SP-D connection – systolic pressure in the pulmonary artery (r=0.59, p<0.05) and SP-D – the number of bed-days in the IC department (r=0.71, p<0.05) caused complications from the function of external respiration.

Thus, the obtained data will offer to determine the level of SP-D in the blood as a highly informative marker of combined thoracic trauma, and the leading mechanism of complications is the occurrence of oxidative stress with secondary damage to surfactant, which leads to a shift in the concentration of SP-D – lung parenchyma/blood.

#### 4. Discussion

Acute re s piratory distress syndrome/acute lung injury syndrome is one of the most severe forms of acute respiratory failure, which is characterized by rapidly increasing changes in the lungs, persistent hypoxemia and high mortality [14, 15]. This condition is not considered as a separate nosological form, it is always a complication of other serious injuries or diseases. There are extrapulmonary variant, which usually occurs on the 2–3rd day as a complication of processes that do not begin with lung damage, and pulmonary, which develops as the final stage of primary lung damage, such as pneumonia [23, 24]. At the same time, patients with combined thoracic trauma in the context of these data are the most complex contingent, as they simultaneously affect the function of external respiration of all known mechanisms of development.

Today, the vast majority of algorithms for the treatment of this pathogenetic condition is characterized by low efficiency [22], which for modern science is a problem that needs to be addressed quickly.

Currently, the diagnosis and determination of the severity of this complication is based on the use of Berlin criteria, including clinical, radiological and physiological indicators that characterize the presence of bilateral pulmonary edema and the severity of blood oxygenation disorders [18, 19]. The Berlin criteria, of course, solve the problem of verifying acute lung injury, but do not allow to detect the development of the pathological process at an early stage and gradually assess it on the main links that underlie existing and promising methods of pathogenetic therapy [17]. Thus, modern diagnostic methods do not allow to trace the development of the main pathological changes, it is reasonable to prescribe pathogenetic therapy, evaluate its effectiveness and prognosis.

In the last decade, a significant amount of experimental and clinical research has focused on studying the diagnostic and prognostic potential of molecular biomarkers, which have significant potential for identifying damage to lung structures and assessing the severity of systemic inflammatory response syndrome in respiratory distress syndrome [32]. The scope of biomarkers is expanding every year and includes not only their use as indicators of the presence or absence of the disease, but also to determine its severity [31]. In this context, high hopes for the use of biomarkers are associated with the solution of the problem of early diagnosis of acute lung injury syndrome, when there are no radiological signs of bilateral edema and critical disorders of blood oxygenation. Another relevant area of research on biomarkers should be considered their implementation to determine the tactics of treatment and assess its prognosis.

It is important to study the structural elements of the surfactant, as an early indicator of the degree and severity of lung damage. It is the surfactant protein SP-D that is the leading one due to its properties to regulate normal lipid recirculation and to program macrophages for M1 and M2 type [30].

Taking into account the data obtained during the analysis of the dynamics of SP-D in the blood of patients with combined thoracic trauma on the 1st, 3rd, 7th and 12th day of hospital stay, and determined the correlations between its level in the blood, systolic pressure in the pulmonary artery number of bed-days in the IT department, can be predicted as the leading pathogenetic mechanism of acute lung injury is oxidative stress.

**Study limitations**. The small number of studied patients does not allow to spread the obtained data to the entire population of patients, which requires further research.

**Prospects for further research**. Due to the increased risk of complications in patients with combined thoracic trauma, it is important to deeply study the sensitive markers of the functional state of the pulmonary parenchyma to determine within the restrictive regimen

of infusion therapy the most pathogenetically justified components.

## 5. Conclusions

1. In patients with combined thoracic trauma, it is important when planning patient management tactics to diagnose the content of surfactant protein SP-D in the blood throughout the stay in the intensive care unit.

2. The l e vel of SP-D in the blood of patients with combined thoracic trauma is a highly informative diagnostic marker of the functional state of the lung parenchyma (surfactant). An increase in its numbers three times in d icates the beginning of the development of acute lung injury syndrome (exudative phase). Reducing its level during the respiratory distress syndrome by half the values in the exudative phase indicates the beginning of the proliferative phase and improvement of patients.

3. The leading mechanism for the development of acute lung injury syndrome in patients with combined thoracic trauma is oxidative stress, so the appointment of ceruloplasmin as an adjunct to the standard protocol of intensive care is pathogenetically justified.

#### **Conflict of interest**

The authors declare that they have no conflicts of interest.

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