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The Use of Selective Hemosorption of Lipopolysaccharides in the Complex Treatment of Sepsis

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BACKGROUND Sepsis and septic shock are formidable and complications in surgery with mortality 20–50%. In the pathogenesis of sepsis, a significant role belongs to bacterial endotoxin (LPS — liposaccharide).

AIM OF STUDY Assessment of the efficacy of selective lipopolysaccharides hemosorption (SLH) in treatment of sepsis.

MATERIAL AND METHODS We examined 65 patients with developed sepsis or suspected presence of gram-negative infection. Patients were retrospectively divided into two groups. In Group 1, 27 patients received Polymyxin B hemoperfusion using Toraymyxin cartridges. In Group 2 (38 patients), adsorber Alteco (LPS-A) was used.

RESULTS It was established that 28-day mortality was 11.1% in Polymyxin group and 28.9% in LPS group A, p = 0.091, 60-day mortality was 33.3 and 55.3%, respectively (p=0.065).

The use of SLH contributed to a decrease in the activity of endotoxin (EAA) from 0.52 (0.39; 0.65) to 0.40 (0.36; 0.57) EU (p=0.330) in Polymyxin group and from 0.59 (0.42; 0.72) to 0.54 (0.40; 0.81) EU (p = 0.981) in the LPS-A group. At the same time, the level of procalcitonin (PCT) in the blood statistically significantly decreased from 8.4 (3.6; 29.0) to 4.8 (1.9; 36.3) ng/ml (p=0.0117) only in the LPS-A group. The level of C-reactive protein (CRB) in the blood statistically significantly decreased only in the Polymyxin group, from 205 (154; 264) to 162 (106; 202) mg/L (p<0.001). After SPH procedures, there was a tendency to a decrease in the level of blood cytokines in both groups.

CONCLUSION 1. The trend of better survival among patients was noted during hemoperfusion when using Polymyxin B in comparison with the results of adsorption of lipopolysaccharide with Alteco cartridges: so, 28-day mortality was 11.1 and 28.9%, respectively (statistically not significant).

2. As a result, the procedure of selective lipopolysaccharides hemosorbtion on hemosorbents with Polymyxin B in blood significantly decreased level of C-reactive protein (21%), there was statistically insignificant decrease in the level of endotoxin activity (23.1%), lipopolysaccharide binding protein (21.6%), procalcitonin (2.4 times), presepsin (20%), as well as the level of interleukin-6 (3.4 times) and interleukin-10 (1.6 times) . Adsorption of lipopolysaccharide with Alteco cartridges leads to a statistically significant reduction of procalcitonin in blood (1.8 times), and statistically insignificant decrease of: endotoxin activity (9.3%), lipopolysaccharide binding protein (28.6%), interleukin-6 (3.8 times), interleukin-10 (7.1 times) and soluble receptor to interleukin-2 (2.2 times).

Keywords: sepsis, septic shock, endotoxin lipopolysaccharide selective hemosorbtion, Polymyxin B hemoperfusion, LPS adsorber Alteco, extracorporeal hemocorrection

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CRP - C - reactive protein
EAA - endotoxin activity assay
IL - interleukin
IL-2R - soluble receptor for IL-2
K-M - analysis of survival of patients with the use of the of Kaplan-Meier method
LBP - lipopolysaccharide - binding protein
LPS - lipopolysaccharide
LPS-A - adsorption of lipopolysaccharide using Alteco columns
NF-kB - nuclear factor kappa B
PCT - procalcitonin
PMX - Polymyxin-B
PSP - presepsin
RCT - randomized controlled trial
SHL - selective hemosorption of lipopolysaccharides
TLR4 - Toll-like receptor 4
TNF α - tumor necrosis factor α
U - nonparametric Mann – Whitney test
W - nonparametric Wilcoxon test

Sepsis and septic shock are not rare and often fatal complication of many surgical diseases and severe concomitant injury. Thus, in the USA [1] in 2014 sepsis was detected in 6% of 2.9 million hospitalized patients, of which septic shock developed in 15.8% of cases, mortality in the hospital was 15%, and 6% of patients were transferred to hospices. When comparing the results of two multinational, multicenter study (*SOAP* and *ICON*) we revealed, that the occurrence of sepsis in resuscitation and intensive therapy units has increased from 29.6% to 31.9% for 10 years from 2002 to 2012 with a reduction in mortality from 32.2% to 25.1% respectively [2].

According to the results of the 3rd conciliation conference on the definition of sepsis and septic shock [3], sepsis is "the state dangerous for life, when in the result of dysregulated response of the immune system of the body to an infection own tissue and organs are damaged." In sepsis, hyperactivation of some parts of the immune system and suppression of others occurs simultaneously. It was found, that mechanical and surgical injury, as well as massive infection cause early hyperinflammatory response. Later, with secondary endogenous or exogenous infection against the background of an imbalance in the cellular and humoral links of the immune system, the clinical picture of sepsis develops. The lack of adequate inflammatory response due to hyperproduction of inflammatory cytokines often leads to "immune paralysis" [4-6].

In the pathogenesis of sepsis the significant role belongs to bacterial endotoxin, representing a lipopolysaccharide (LPS), which amounts to 75% of the outer membrane of gram-negative bacteria. In the bloodstream it binds lipopolysaccharide - binding protein (LBP) and forms a complex, which interacts with *CD*-14-receptor of mononuclear phagocytes, increasing the sensitivity of these cells to LPS by 100-1000 times, that occurs with the participation of myeloid differentiation factor-2. As a result of phagocytosis activation in blood the concentration of presepsin (PSP). In addition, LPS activates toll-like receptor 4 (*TLR* 4), which leads to phosphorylation of an inactive complex of inhibitory protein *kB* and other transcription factors that trigger nuclear factor kappa B (*NF-kB*). The genes for cytokines, chemokines, coagulation factors, complement, acute phase proteins, and nitric oxide synthase contain *NF-kB* binding sites in their promoter zones [7]. As a result, there is a change of the transcription of genes, responsible for cellular and humoral components of the systemic inflammatory response, mechanisms producing cytokines and other factors of inflammation are triggered. LPS, modifying the expression of genes, activates endothelial cells and white blood cells, which produce proinflammatory mediators (particularly TNF α, interleukin - IL-1, IL-6, IL-8, and interleukin-12), and also starts the process of activation of the complement and blood clotting [8]. Proinflammatory cytokines and mediators of inflammation lead to the release of the active metabolites of oxygen, in fact include oxides of nitrogen, development of uncontrolled oxidative explosion in polymorphonuclear neutrophils and macrophages, which renders damaging action both on the endothelium and cells of organs and tissues, and finally leads to organ failure [9-11].

That is why elimination of LPS from using selective hemosorption lipopolysaccharides (SHL) is of considerable interest, since the key element of the pathogenesis of sepsis is triggered. Today the following sorbents are mostly used in the world and Russia. First is Toraymyxin column, where endotoxin specifically binds with polymyxin-B, adsorbed on the polystyrene membrane (PMX). Since 1994 over 150 000 procedures have been performed all over the in world using *PMX* in patients with sepsis and septic shock [12, 13]. The second is selective hemosorbent, where sorption of LPS is carried out by binding it to a synthetic peptide *HAE* 27 with high affinity to endotoxin - LPS - adsorber Alteco (LPS-A).

When analyzing the literature we haven't found work, comparing the effectiveness of using various selective sorbents for sorption of LPS.

The aim of this study was to evaluate the effectiveness of the use of SHL in the complex treatment of sepsis.

Objectives: to conduct comparisons of outcome of treatment in patients with the use of two selective hemosorbents, to rate dynamics markers of systemic inflammation when carrying out SHL.

MATERIAL AND METHODS

The study included 65 patients (37 men and 28 women), treated at N.V. Sklifosovsky Research Institute for Emergency Medicine from January 2008 to July 2018, where the primary disease was complicated by the development of sepsis and septic shock. The reason for inclusion of extracorporeal hemocorrection (SHL) was the following: confirmed or suspected gram-negative sepsis, septic shock, multiple organ dysfunction, and the level of procalcitonin (PCT) in blood over 2 ng/ml. Patients were retrospectively divided into two groups, depending on the used columns for SHL. In one group (27 patients, *PMX group*), Polymyxin-*B* with *Toraymyxin* «*PMX*-20R» columns was used, *(Toray Industries, Inc., Japan*) for the removal of endotoxin, in the other group (38 patients, LPS-A group) *Alteco® LPS Adsorber* (*Alteco Medical AB*, Sweden) was used. *The Aquarius, NIKKISO* (Japan) and *Multifiltrate, Fressenius Medical Care* (Germany) were used for the continuous of renal replacement therapy and extracorporeal blood correction in the mode of a hemoperfusion.

For the statistical processing of the obtained results *SPSS* 19.0 (*SPSS, Inc.*) And *STATISTIKA* 12.0 (*Stat.Soft, Inc.*) were used. All samples were tested on the normality of distribution with the help of the Kolmogorov-Smirnov test. The median and interquartile range were calculated. For comparison of variables with normal distribution paired Student't t-test was used (for linked and unconjugated samples). Upon distribution, other than normal, nonparametric Mann-Whitney (*U*) test was used for unconjugated samples, and Wilcoxon (*W*) was used for linked samples. To analyze the survival rate of patients, the Kaplan-Meier (K-M) method was used. For comparison of nominative data Chi - square (χ^2) was used. The obtained results were considered statistically significant at the level of $p < 0.05$.

Groups didn't differ statistically significantly (Table 1) regarding age: 37.0 (27; 59) years in PMX group and 41.0 (29; 54) - in LPS-A group ($p = 0.852$, *t* - test for independent samples), gender ($p = 0.486$, χ^2 test) and the severity of condition of patients according to *APACHE* II - 23.0 (16; 25) and 21.0 (16; 24) points respectively ($p = 0.793$, *U* - test). Regarding the source of sepsis, groups also statistically significantly did not differ, apart from subgroup of severe acute pancreatitis in the phase of septic complications, which frequency was 33% in PMX group and 13.2 % ($p = 0.0512$, criterion χ^2) in LPS-A group.

Table 1

Characteristics of patients in the compared groups

Indicators	*Polymyxin* Group (*n*=27)	LPS-A group (*n*=38)	*p*	Criteria
Age, years	37.0 (27; 59)	41.0 (29; 54)	0.852	Student's t-test for independent samples
Gender, m/f	14/13	23/15	0.486	χ^2
APACHE II, score	23.0 (16; 25)	21.0 (16; 24)	0.793	*U*
Peritonitis, *n* (%)	2 (7.4)	8 (21.1)	0.1330	χ^2
Mediastinitis, *n* (%)	2 (7.4)	2 (5.3)	0.7230	χ^2
Severe damage with concomitant injury of 3 or more anatomical regions (*ISS* over 25), *n* (%)	7 (25.9)	7 (18.4)	0.4683	χ^2
Severe acute pancreatitis, *n* (%)	9 (33.3)	5 (13.2)	0.0512	χ^2
Other sources of sepsis, *n* (%)	7 (25.9)	16 (42.1)	0.1789	χ^2
Of these, after organ transplantation, *n* (%)	3 (11.1)	5 (13.2)	0.8045	χ^2
Number of treatments	1.0 (1; 2)	1.0 (1; 2)	0.441	*U*
Duration of procedures, hours	4.0 (3.0; 7.5)	3.0 (2.0; 5.0)	0.263	*U*
Blood flow rate, ml/min	120 (110; 140)	100 (100; 120)	0.0002	*U*
Beginning of procedures from the moment of hospitalization, days	9.5 (5.0; 27)	11.0 (4.0; 28.0)	0.989	*U*

Notes: data presented with median and interquartile range (25 %th, and 75 th percentiles). χ^2 — chi-square test; LPS-A — lipopolysaccharide adsorption using Alteco cartridges; *n* — number of patients; *U* — nonparametric Mann-Whitney test

A total of 44 *PMX* procedures and 56 LPS-A hemoperfusion procedures were performed. In both groups 1 to 5 treatments were performed normally with 24-hour interval, 1.0, median (1; 2) ($p = 0.441$, *U* - test). The duration of SHL was 4.0 (3.0; 7.5) and 3.0 (2.0; 5.0) hours respectively ($p = 0.263$, *U* - test). The time gap between hospitalization and the first procedure - 9.5 (5.0; 27) and 11.0 (4.0; 28, 0) days - did not differ statistically significantly ($p = 0.989$, *U* - test). The rate of blood flow in both groups was from 90 - 160 ml / min, in *PMX* group the rate of blood flow was statistically significantly higher than 120 (110 ; 140) as compared to 100 (100; 120) ml / min in the group of LPS-A ($p = 0.0002$, *U* - test). Anticoagulation was performed with constant infusion of heparin, 10-20 units / kg / hour, under the control of the time of coagulation of blood.

The diagnosis of sepsis and septic shock was set on the basis of conciliation conference "Sepsis-3" [3]. We calculated 28-, 60-, 90- day and hospital mortality. The duration of stay of patients in hospital was compared among survivors.

The activity of endotoxin *«Endotoxin Activity Assay» (EAA)* in the blood was evaluated with the help of test - systems *«Spectral Diagnostics Inc.»* (Canada) and *"Smartaline TL"* luminometer (*Berthold*, Germany). To assess the severity of systemic inflammation we measured concentration in the blood *C* - reactive protein (*C*RP), PCT, PSP, IL-6, IL-10, soluble receptor to IL-2 (IL-2R) and LBP. Blood sampling was performed before and at within 24 hours after SHL. The concentration of the PCT, interleukin-6 and interleukin-10 was determined by enzyme immunoassay method using the set of reagents "Vector - Best" in a microtiter plate reader *Synergy HT* (*Bio-Tek Instruments*, United States). CRP was investigated on automatic analyzer *BN «ProSpec»* (*Dade Behring*, Germany). LBP and IL-2R were determined with *IMMULITE* 2000 automatic immunochemiluminescence analyzer (*DPC*, USA). The level of PSP was measured on immunochemiluminescence analyzer *PATHFAST* (Japan).

EAA was determined when conducting 25 procedures of SHL, IL -2R and LBP - at 11, IL-6 - at 34, IL-10 - at 12, PSP - at 26, PCT - at 88 and *CR*P - at 93 procedures.

RESULTS

When comparing mortality we revealed, that in group *PMX* there was a marked trend of better survival as compared to LPS-A group (Table 2) (Figure 1.): so, the 28-day mortality was 11.1% and 28.9% ($p = 0.091$, K - M), 60 days - 33.3% and 55.3% ($p = 0.065$, K - M), 90 days - 37.0% and 57.9% ($p = 0.069$, K - M), and the hospital mortality - 44.4% and 57.9%, 57.9%, respectively ($p = 0.147$, K - M). Only in the *PMX* group hospital mortality rate was at 3.4% lower than calculated by a scale *APACHE* II - 47,8 (23,5; 53.3)%, and up to 60 days remained below at 14.5%. In LPS-A group lethality already on the 60 th day was 16.4% greater than a calculated, equal to 38.9 (23.5; 49.7)%, a hospital - 19% greater. Terms of treatment of surviving patients in hospital statistically significantly did not varied and were 90 (63; 116) days in a group of *PMX*, 96 (47; 131) days in LPS-A ($p = 0.937$, *U* - test).

Table 2

Treatment outcomes in patients with sepsis

Indicators	*Polymyxin* Group (*n*=27)	LPS-A group (*n*=38)	*R*	Criteria
Estimated mortality according to the *APACHE* II scale ,%	47.8 (23.5; 53.3)	38.9 (23.5; 49.7)	0.634	*U*
28-day mortality,%	3 (11.1%)	11 (28.9%)	0,091	K-M
60-day mortality,%	9 (33.3%)	21 (55.3%)	0,065	K-M
90-day mortality,%	10 (37.0%)	22 (57.9%)	0,069	K-M
Hospital mortality,%	12 (44.4%)	22 (57.9%)	0.147	K-M
The duration of stay of surviving patients in the hospital, days	90 (63; 116)	96 (47; 131)	0.937	*U*

Notes: data presented with median and interquartile range (25 %th, and 75 th percentiles). K-M — Kaplan–Meier method; LPS-A — lipopolysaccharide adsorption using Alteco cartridges; *n* — number of patients; *U* — nonparametric Mann-Whitney test

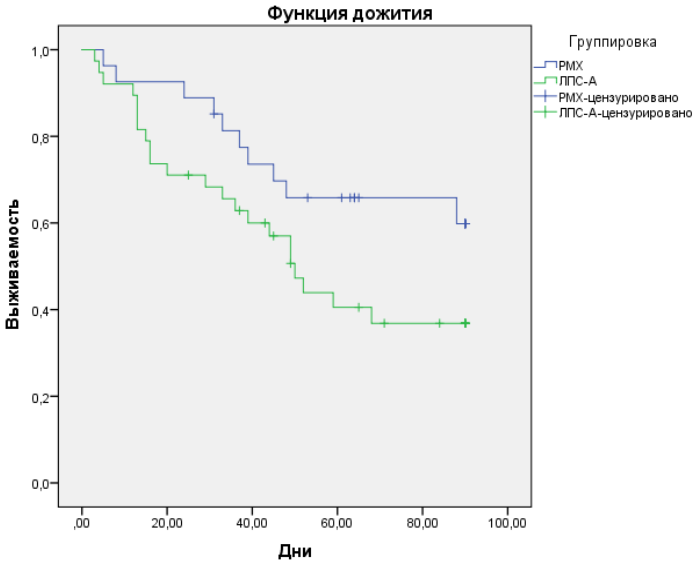

Fig. 1. Survivorship function (90 days) depending on the type of selective hemosorbent
Notes: LPS - A - lipopolysaccharide adsorption using Alteco cartridges; PMX - polymyxin

It was found (Table 3), that in patients with sepsis marked increase in the activity of endotoxin to procedures in both groups: median was 0.52 (0.39; 0.65) *EU* in *PMX* group and 0.59 (0.42; 0 72) *EU* in LPS-A group. SHL contributed to reduce the level of endotoxin and in blood to 23.1% in the *PMX* group (p = 0.330, *W* - test), which is practically not observed in LPS-A group (p = 0.981, *W* - test).

Table 3

The effect of selective liposaccharides hemosorption on indicators of systemic inflammation in patients with sepsis

	Polymyxin B (*n*=44)			LPS-A (*n*=56)		
Indicators (normal range)	Initially	After sorption	*p*	Initially	After sorption	*p*
EAA , EU (0.1–0.4)	0.52 (0.39; 0.65)	0.40 (0.36; 0.57)	0.330	0.59 (0.42; 0.72)	0.54 (0.40; 0.81)	0.981
LBP, mcg/ml (2.2 ÷ 11.4)	49.5 (26.8; 60.3)	38.8 (24.1; 55.5)	0.362	50.3 (49.3; 72.3)	39.1 (27.2; 52.8)	0.169
PCT, ng/ml (0 ÷ 1.0)	17.5 (2.4; 56.6)	7.4 (3.6; 47.2)	0.509	8.4 (3.6; 29.0)	4.8 (1.9; 36.3)	0.0117
CRP, mg/L (0 ÷ 5)	205 (154; 264)	162 (106; 202)	< 0.00 1	192 (152; 270)	195 (128; 270)	0.432
PSP, pg/ml (0 ÷ 337)	1879 (578; 3893)	1504 (509; 3786)	0.849	2047 (981; 3890)	3891 (1765; 4963)	0.282
IL-6, pg/ml (0 ÷ 10)	2900 (1066; 6000)	861 (300; 2900)	0.505	710 (82; 3954)	186 (50; 3509)	0, 347
IL-10, pg/ml (0 ÷ 20)	62.7 (11.9; 196.9)	39.1 (17.1; 77.3)	0.282	67.7 (17.6; 249.9)	9.5 (6.3; 67.8)	0.221
IL-2R, U/ml (158 ÷ 623)	2245 (924; 5722)	2680 (814; 4428)	0.75	2263 (1207; 3794)	1025 (807; 2031)	0.233

Notes: data presented with median and interquartile range (25% ^{th,} and 75 th percentiles). To compare the indicators, initially and after sorption, the Wilcoxon test was use d within groups, and the Mann– Whitney test was used between groups. EAA - endotoxin activity; CRP - C-reactive protein; LBP, lipopolysaccharide binding protein; LPS-A - lipopolysaccharide adsorption using Alteco cartridges; *n* - number of patients; PCT, procalcitonin; PSP - presepsin; *U* - nonparametric Mann-Whitney test

Initially, in both groups, the level of LBP, an acute phase protein and endotoxin carrier with a molecular weight of about 50 kDa, was 5 times higher than the upper limit of normal values. After SHL, it decreased in the *PMX* group by 21.6% (p = 0.362, *W* - test), and by 22.2% in the LPS-A group (p = 0.169, *W* - test).

The level of PCT in the blood prior to the procedures was increased in both groups up to 17.5 (2.4; 56.6) ng / ml in *PMX* group and 8.4 (3.6; 29.0) ng / ml in LPS-A group. After SHL it statistically significantly decreased by 1.75 (p = 0.0117, *W* - test) only in LPS-A group, in contrast to *PMX* group, where a decrease by 2.4 times was statistically insignificant (p = 0.509, *W* - test). PCT is a polypeptide with molecular weight 12793 Da and the period of half-life of 22-35 hours, its content in blood significantly increased 3 hours after the development of systemic inflammatory reactions and quickly reduced as the activity of the inflammatory process decreased [17].

*C*RP consists of 5 monomers with a molecular mass of 115 kDa, appears in the circulation 4-6 hours after the beginning of inflammation, its significant amount circulates in blood in the form of monomers with a molecular hydrochloric mass of 22-25 kDa [5]. The *C*RP level decreased statistically significantly by 21% only in the *PMX* group (p <0.001, *W* - test).

In our study, the level of PSP in blood was increased in both groups: median was 1879 pg / ml in PMX group and 2047 pg / ml in LPS-A group. The use of SHL caused multidirectional changes in the PSP. While its level became 20% less in PMX group (p = 0.849, *W* - test), in the group of LPS-A the concentration of PSP became 190% greater (p = 0.282, *W* - test). PSP is a protein, with a molecular mass of 13 kDa, fragment of membrane receptor of monocytes *mCD* 14 formed at phagocytosis of bacteria, its level in blood increases 1.5 hours after the development of sepsis.

Baseline levels of IL-6, one of the most important pro-inflammatory cytokines (a glycoprotein with a molecular weight 19-24 kDa), was 4 times higher in the PMX group as compared to LPS-A group, 2900 (1066; 6000) pg / ml and 710 (82; 3954) pg / ml, respectively (p = 0.102, *U* - test). After SHL its reduction was noted in *PMX* and LPS-A groups by 3.4 and 3.8 times respectively.

IL-10 is an anti-inflammatory cytokine with a molecular weight of 17–21 kDa. After SHL more pronounced decrease in IL-10 was observed in LPS-A group, a 7.1-fold (p = 0.221, *W* - test) than in PMX group - 1.6-fold (p = 0.082, *W* - test). The concentration of the soluble receptor for IL-2 consists of three different polypeptide subunits: IL-2R *a*, IL-2R *b* and IL-2R *g*, forming membrane-bound protein of molecular weight of 55-65 kDa. Its level after the procedure SHL increased in PMX group by 19.4% (p = 0.75, *W* - test) and decreased by 2.2 in LPS-A group (p = 0.233, *W* - criterion).

At the same time in 6 patients of both groups after SHL concentration of tested biomarkers increased, while this clinical signs of intoxication on the background of the ongoing septic process sustained (Fig. 2). In all these patients, the septic process was caused with *S. aureus.*

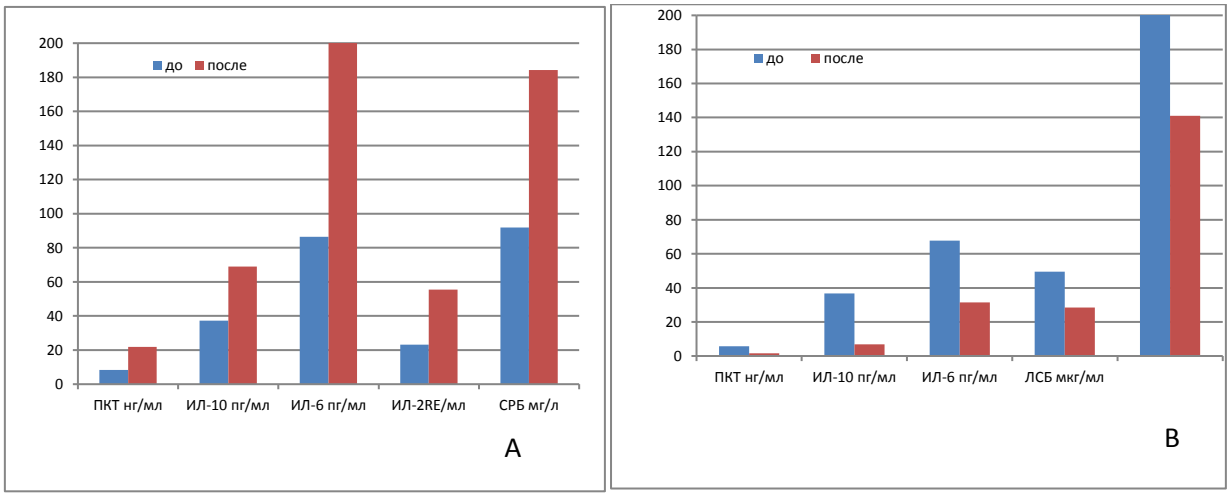

Fig. 2. The dynamics of sepsis markers depending on the etiology of infectious process. A - Gram-positive microflora; B - Gram-negative microflora

DISCUSSION

Over the last 10 years a number of works was published, assessing the efficiency of using the selective adsorption of endotoxin in patients with sepsis and septic shock. These studies mostly concerned the use of hemoperfusion with the help of *PMX* columns. First of all, this is multicenter, randomized, controlled study (RCT) *EUPHAS*, published in 2009, in which *PMX* was used in patients with abdominal sepsis [14]. The authors noted a statistically significant reduction in the severity of organ dysfunction in the group with *PMX* - hemoperfusion, mainly due to the improvement of hemodynamic and renal function, reduction in 28-day mortality rate, which was 32% in the study group by comparison with 53% in the control group. The study was discontinued on the recommendation of the ethics committee. In 2015 the results of RCTs *ABDOMIX* were published [15], which are not shown to improve survival of patients with abdominal sepsis when using *PMX* - hemoperfusion. The 28-day mortality rate in the *PMX* group was 27.7% and 19.5% in the control group. The authors have not mentioned difference in reducing the severity of organ dysfunction on day 3, 7 and 14. However, in this study there was a significant number of issues in connection with the problems with carrying out procedures in 30.2% of patients (thrombosis loop and other technical problems, hemodynamic instability). In 2016, the data of *PMX EUPHAS* 2 register was published [16], where the results of *PMX* - hemoperfusion in 357 patients were presented from 2010 to 2014 in 57 centers from Europe and Asia. The most common source of sepsis and septic shock was abdominal infection (44%), in 17.6% - pulmonary infection. The 28-day mortality was 45.5%, if the treatment started within 24 hours after diagnosis of abdominal sepsis, the mortality was 34.5%, which corresponded to the results of *EUPHAS* studies. The authors noted a variety of mortality when compared to centers in Europe and Asia - so, 28-day lethality was 41.2% and 65.5% respectively.

Results of treatment in the *PMX* group, presented in this study, are consistent with data of the European subgroup *EUPHAS* 2, with a similar gravity condition on a scale *APACHE* II (23.0 and 21.8 points) hospital mortality was 44.4% and 46.8% accordingly. In 2018 the results of the RCT *EUPHRATES* were published [17]. The study included 450 patients with septic shock and level *of EAA* above 0.6 units. In the primary analysis, 28-day mortality in the primary and control groups (37.7% and 34.5%, respectively) did not differ, there were no differences in the subgroup with severity of organ dysfunction for *MODS* more than 9 points (44.5% and 43 , 9%, respectively). Only in the subsequent analysis, excluding patients with *the EAA* more than 0.89 units [18], the authors found a statistically significant difference in 28-day mortality - 26.1% and 36.8%, respectively. It should be noted, that in the study *EUPHRATES*, although at high indices *of EAA*, bacteraemia was detected only in 33% of patients in group *PMX* and in 28.1% - in the control group, gram-negative microorganisms were detected in 23.9% and 13.3% of cases, respectively. Significant differences in the level *of the EAA* from the patients of both groups at baseline, after 10 and 24 hours after finishing two procedures: 0.79 ± 0.13 and 0.77 ± 0.13 units 0.71 ± 0.23 and 0.71 ± 0.23 and 0.66 ± 0.21 and 0.65 ± 0.22 units, accordingly. It seems that in some cases, the high performance of the EAA is associated with bacterial translocation from the intestine.

Considerably less work is devoted to the study of results of LPS-A - hemoperfusion. Thus, in article of Poland [19], in contrast, its use resulted in a statistically significant reduction in *the EAA* through 24 hours after the procedure - from 0.70 (0.66; 0.77) to 0.56 (0, 43; 0.77). At the same time there were no decrease in mortality, which was 33% in the main group, compared to 30% in the control group.

Our results are consistent with the published data on reducing the concentration of acute-phase proteins, cytokines and chemokines (IL-6, IL-8, IL-10, TNF-α, *High-mobility group box* 1) in the blood after SHL in patients with sepsis, septic shock after surgical interventions and transplant kidneys [20-24]. However, in the published study (2017) [25] the reduction of cytokines (TNF-α, IL-1β, IL-6, IL-10, IL-1*RA*) after procedures *PMX*-hemoperfusion were accompanied with a similar decrease of cytokines in the control group, except IL-17*A*. Thus, for example, the initial level of IL-6 in the main and control groups statistically significantly did not differ (2199 and 2035 pg / ml), decreasing after conducting two sessions *PMX* to 339 pg / ml and 197 pg / ml, respectively.

CONCLUSION

Our data confirm the possibility of applying selective hemosorption of lipopolysaccharides in patients with gram-negative sepsis and septic shock for elimination of lipopolysaccharides, reduction of cytokines in blood occurs both due to binding endotoxin, initiating the inflammatory cascade, and their sorption by hemosorbents. Mostly this is associated with selective hemosorption of lipopolysaccharides with columns, containing Polymyxin B. At the same time, while using Alteco cartridges, we found an increase in the level *C* - reactive protein and presepsin in the blood, that may be associated with their less sorption capacity. Application of Polymyxin-B is accompanied by improved survival of patients as compared to a group of lipopolysaccharide adsorption with Alteco columns. However, our study is limited by the retrospective type and small number of observations of the level of endotoxin activity, the concentrations of cytokines, and a series of markers of systemic inflammation, which requires further study.

FINDINGS

1. When using Polymyxin we observed best survival as compared to a group of lipopolysaccharide adsorption with Alteco columns: 28-day mortality was 11.1% and 28.9%, 60-day - 33.3% and 55.3%, and hospital mortality - 44.4% and 57.9%, respectively. The differences were not statistically significant.

2. The use of selective hemosorption of lipopolysaccharides in the complex treatment of sepsis according to laboratory studies is accompanied by a decrease in the activity of the systemic inflammatory response. As a result, hemoperfusion with Polymyxin - *B* in blood statistically significantly reduced the level of *C* - reactive protein - 21% greater, a statistically insignificant reduction level activity of endotoxin was observed - for 23.1%, lipopolysaccharide - binding protein - 21.6 %, procalcitonin - 2.4 times, presepsin - 20%, but also the level of the interleukin-6 - 3.4 times and interleukin-10 - by 1.6 times. Lipopolysaccharide adsorption with Alteco columns led to a statistically significant decrease in the level of procalcitonin in blood by 1.8 times, statistically insignificant decrease in the level of activity of endotoxin - 9.3%, lipopolysaccharide - binding protein - 28.6%, interleukin - 6 - 3.8 -fold, interleukin-10 - 7.1 -fold, as well as a soluble receptor to interleukin-2 - by 2.2 times.

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