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Sepsis-associated microbial metabolites as an indicator of complications during extracorporeal therapy in cases of sepsis and septic shock in children

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INTRODUCTION & AIM

Modern blood purification technologies are widely used in intensive care to treat patients with sepsis and septic shock. Mortality was significant and increased as organ failure progressed, therefore, further evaluation of the effectiveness of extracorporeal therapy for severe sepsis and septic shock in children is necessary.

The three most significant aromatic metabolites are called sepsis-associated, these are phenyllactic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylacetic acid. In 2018, an article was published on the involvement of aromatic microbial metabolites in the development of septic shock, which presented a hypothesis about the mechanism and clinical evidence [1].

The ability of sorbents to bind aromatic microbial metabolites associated with sepsis is well known due to in vitro experiments [2]. In the clinical pediatric study described above, we were able to confirm that the use of Efferon LPS Neo for hemosorbtion in children significantly reduces the concentration of all three sepsis-associated aromatic microbial metabolites (AMMs).

AIM To evaluate the change in the concentration of sepsis-associated microbial metabolites when using the method of extracorporeal therapy of severe sepsis and septic shock in children.

MATERIALS AND METHODS

The hemosorption was performed using a device for extracorporeal blood purification (Fig. 1), Efferon LPS NEO (Efferon Company, Moscow, Russia) for children with sepsis and septic shock (n=30). Patients were included in the study no later than 12 hours after the diagnosis of sepsis/septic shock. The procedure known as hemosorption was performed using a device for extracorporeal blood purification Efferon LPS NEO ((Efferon Company, Moscow, Russia) on the patient in two separate sessions, each lasting approximately 6-12 h, with an interval of 24 h between each treatment. Both sessions lasted 18 (12-23) hours. The study protocol ClinicalTrials.gov ID NCT05707494 is available at Study Details | Lipopolysaccharide Adsorption (Efferon LPS NEO) in Children With Sepsis | ClinicalTrials.gov. The control group of patients had sepsis and septic shock without hemosorption, n=46.

Figure 1. The general diagram of the hemosorption device (A), a photo of the Efferon® LPS NEO pediatric cartridge (B), and the process of blood purification using a sorbent that removes lipopolysaccharide (LPS), cytokines and/or other low-molecular-weight molecules (C).

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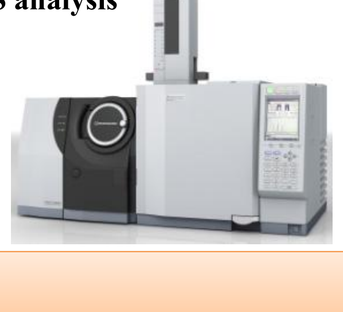
- ✓ **The concentration of metabolites** in blood serum was determined by gas chromatography-mass spectrometry using equipment from Shimadzu, Tokyo, Japan.

Blood serum samples → **Sample preparation:**
- ✓ Adding internal standard
- ✓ Liquid-liquid extraction
- ✓ Evaporation to dryness
- ✓ Silylation
- ✓ Dilute with hexane

→ **GC-MS analysis**



RESULTS & DISCUSSION

The diagnoses in the comparison groups were similar, and on the day of study inclusion, the source of infection was reported as the lungs (54%) or intestines (30%), less commonly the brain (7%), skin/soft tissue (5%), and others. The following microorganisms were also isolated: Klebsiella spp. (22%), Staphylococcus spp. (18%), Pseudomonas aeruginosa (17%), Escherichia coli (15%), Streptococcus spp. (15%), Enterococcus spp. (10%), and others. The effectiveness of hemosorption in children was demonstrated by comparing the main treatment indicators in two groups (hemoadsorption group, n=30, and control group, n=46) on the graph (Fig. 2).

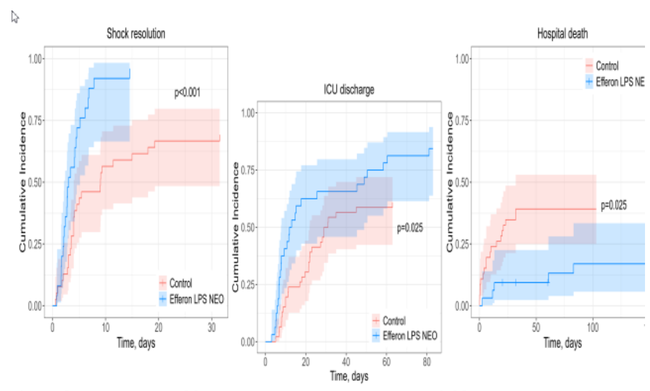


Figure 2. Main result of RCT «Efferon LPS NEO». Differences of group «hemosorption», (blue color) and group «control» (red color) in the duration of septic shock treatment, the length of stay in the intensive care unit, and hospital mortality.

Aromatic microbial metabolites		Before, n=30	After, (n=30)	p-value
Sum of three AMMs, µmol/l	Median	6,5 (3,7; 8,1)	2,3 (1,1; 8,1)	0,020
	Max	25	71	
	Min	1	0,8	
Phenyllactic acid, µmol/l	Median	0,8 (0,6; 1,3)	0,6 (0,3; 1,2)	0,034
	Max	9,1	7,0	
	Min	<0,5	<0,5	
4-Hydroxyphenyllactic acid, µmol/l	Median	2,8 (1,4; 4,6)	0,8 (0,4; 3,7)	0,041
	Max	18	63	
	Min	<0,5	<0,5	
4-Hydroxyphenylacetic acid, µmol/l	Median	1,1 (0,7; 2,7)	0,8 (0,2; 1,2)	0,023
	Max	6,4	14	
	Min	<0,5	<0,5	

Table 1. Statistical comparison of aromatic microbial metabolites using the Wilcoxon t-test at before and after hemosorption in children (n=30) during of the Efferon LPS NEO study.

The analysis of the results showed that initially low blood concentrations of AMMs in children with sepsis/shock may be predictors of rapid improvement in their condition. In the case of an initially high level of AMM in the blood, a rapid decrease during a hemadsorbtion session is accompanied by an improvement in the patient's condition (Tab. 1). Conversely, an increase in the level of AMM and the persistence of high concentrations during the first 3 days indicate the presence of irreversible changes in the body and an unfavorable prognosis.

CONCLUSION

Blood metabolite analysis in sepsis has important clinical implications: elevated and persistently elevated metabolite levels indicate irreversible changes in the body and an unfavorable prognosis. This emphasizes the central role of metabolic monitoring and the importance of microbial metabolism in both understanding and treating sepsis and septic shock in children.

FUTURE WORK / REFERENCES

1. Beloborodova N.V., Sarshor Yu.N., Bedova A.Yu., Chernevskaya E.A., Pautova A.K. Involvement of Aromatic Metabolites in the Pathogenesis of Septic Shock. // SHOCK 50(3):273-279, **2018**, DOI : 10.1097/SHK.0000000000001064
2. Pautova A. K., P. D. Sobolev, A. I. Revelsky. Microextraction of aromatic microbial metabolites by packed hypercrosslinked polystyrene from blood serum. *J Pharm Biomed Analysis* **177**:112883 (**2020**). https://doi.org/10.1016/j.jpba.2019.112883