

THERAPEUTIC APHERESIS IN TROPICAL MEDICINE

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Abstract

The analysis of the most frequent diseases, characteristic for a tropical zone is presented in article. The general factor defining severity of diseases and even their outcome is an endotoxemia with the development of multiple organ insufficiency and medicamentous therapy isn't always effective. It defines indications for an extracorporeal detoxification and the most effective thus is the membrane plasma exchange.

Key words: Chagas' disease, hepatitis, malaria, scorpions, snakebite, Ebola, Denge, Zika, endotoxemia, plasmapheresis.

In the countries of a tropical zone are available a certain group of diseases, specific to this region. Mainly it concerns various infectious diseases caused by the most various causative agents – viruses, bacteria, parasites, and also poisonings caused including the stings of various snakes and insects.

According to WHO in the world of infectious diseases killed every day, up to 16 million people. 30-50 million infections annually registered in Russia. Of these, 10-12% of patients requiring intensive care as a result of infectious toxic shock, toxic encephalopathy and damage other vital organs. The best results are achieved in the presence of intensive treatment before the onset of the critical state [Pokrovsky V.I., 2005].

Virtually no infectious diseases that would not be accompanied by significant intoxication, the latter usually determine the severity of the state, as the main mechanism tanatogenesis significantly affecting the overall outcome. The structure consists of endotoxemia bacterial endo- and exotoxins, products of inflammation and tissue destruction from primary foci of inflammation entering the circulation, secondary metabolic disorders such as, as mentioned above in the description of septic complications.

Clinical manifestations of a variety of infections in many guises, as well as diverse and selective tropism of organ damage as a result of endotoxemia. In some cases the

most severe toxic myocardial lesions (diphtheria), in others – the liver (hepatitis, leptospirosis), kidneys (hemorrhagic fever with renal syndrome), brain (encephalitis, botulism, typhoid, paratyphoid infection). Intestinal infections are often accompanied by dehydration syndrome with disorders of the central and peripheral hemodynamics. However, in most cases combined lesions observed in many organs and systems.

In particular, the development of acute liver failure in **viral hepatitis** contributes to not only the direct impact of viruses that damage the hepatocytes as a cascade of metabolic disorders with accumulation of highly toxic products.

Especially dangerous is the **fulminant form of hepatitis** with massive liver necrosis, which was previously called "acute yellow liver atrophy" [Sorinson S.N., 1998]. Cytotoxic agents while maintaining the active autolysis hepatocytes with suppression of all regeneration processes [Ohnishi H., Nagaki N., 1993]. Developing an "explosion of lysosomes" with the release of active cyto- and proteolytic enzymes causes progressive autolysis and necrosis of hepatocytes with the transition of liver failure in hepato-cerebral form. Accumulation wherein confirmed endotoxins and "paramecium test" accelerated in 4-6 times of death protozoa time in serum of these patients. This explains naturally developing acute renal failure (hepato-renal syndrome), accelerating the onset of multiple organ failure complete. In the genesis of neurological disorders in the course of acute hepatitis leading role played by endotoxins that accumulate with the increase of liver failure. However, we can not exclude the direct damaging effects of hepatitis viruses on elements of the central nervous system, especially as found in the cerebrospinal fluid antibodies against hepatitis C-virus and RNA of the virus, which can be traced as far back as during the year [Caudai C. et al., 1997].

Severe endotoxemia causes *toxic secondary immunodeficiency*, which further weakens the patient's resistance to infection, inhibits the production of specific antibodies. There is evidence that intensive therapy of acute hepatitis C with intravenous high-dose immunoglobulin promotes development in the later period (up to two years) hypogammaglobulinemia, is a predisposing factor for chronic viral infection [Christie J.M. et al., 1997].

All this is particularly acute determines the need for detoxification and apheresis therapy at the height of the manifestations of endogenous intoxication, along with measures to immunostimulation by photo-hemotherapy, using indirect electrochemical oxidation of the blood, in addition to having more detoxification and bactericidal action.

In particular, A.D.Safonov et al. (2003) was performed in 148 patients with plasmapheresis, which amounted to 72.5% of all patients with acute viral hepatitis B and B+C, treated in the intensive care unit. At the same time noted the clarification of consciousness, the disappearance of euphoria, weakness, headaches, drowsiness, tremor, tachycardia, normalize the level of middle weight molecules, increased life expectancy of paramecium. In the absence of positive dynamics was carried out repeated sessions of plasmapheresis. L.J. Li et al. (2005) positive results achieved also during of membrane plasmapheresis is the bulk removal plasma up to 3500 ml .

Upon the occurrence of hepatic coma it was most effective membrane plasmapheresis with removal of up to 5 liters of plasma, thereby lowering levels of bilirubin up to 40%, ammonia 70%, methionine, phenylalanine and tyrosine on 60% and 20% of endotoxins. Unlike hemodialysis or hemosorption with membrane plasmapheresis more fully removed high-toxic products, including autoantibodies and immune complexes formed in severe hepatitis B and aggravating hepatocytes damage [Valbonesi V., 1986]. It is possible also the combined application of hemosorption and a plasma exchange at the treatment of the fulminant liver failure complicated by hepatotoxic encephalopathy [Huang Y.K. et al., 2012; Li M.Q. et al., 2014]. In Japan at an acute liver failure the plasma exchange is applied also [Nakanishi T. et al., 2014].

Severe forms **iktero-hemorrhagic leptospirosis** is often accompanied by an infectious-toxic shock with hemorrhagic syndrome on 5-6th day of the disease. With plasmapheresis managed reduce the incidence of intoxication. In particular the intoxication index LII after the first plasmapheresis decreased 2.4 times, an improvement of coagulation, especially when DIC under anticoagulation. Plasmapheresis also prevented the development of multiple organ failure [Gorodin V.N., 2003; Cerdas-Quesada C., 2011]. M.Valbonesi (1986) with the help of massive plasmapheresis with removal of up to 2.8 liters of plasma was also able to stop acute renal-hepatic failure in 33 of 36 patients. Plasmapheresis was more effective than hemodiafiltration [Tse K.-C. et al., 2002].

In recent years, not only in Africa but also in other parts of the world, the cases of the disease with fever caused by **West Nile virus**, which crosses the blood-brain barrier and causes severe encephalitis with frequent fatal consequences. There is even believed that Alexander the Great died in Babylon at the age of 32 in 2 weeks from such fever [Marr J.S., Calisher C.H., 2003]. Specific therapy has not yet been worked out.

However, in the pathogenesis of the disease plays a role not only direct viral damage to neural structures, but also a general toxic effects [Lim S.M. et al., 2011], that is an indication for extracorporeal detoxification, especially fatalities that precedes the development of severe respiratory distress syndrome [Morrey J.D., et al., 2012]. But after recovery remains quite severe neurological disorders by type of systemic autoimmune demyelinating disease with severe muscle weakness [Cook R.L. et al., 2010; Loeb M. et al., 2011; Leis A.A., Stokic D.S., 2012], which also raises the question about the use of apheresis therapy. And it is valid, by means of a course of a plasma exchange it is possible to reach considerable improvement of the neurologic status [Cooper C.J., Said S., 2014].

With such viral disease such as **hemorrhagic fever with renal syndrome** is characterized by a development of hemorrhagic syndrome on the background of infectious-toxic shock and acute renal failure [Rabinowitz V.I. et al., 2003]. When using plasmapheresis in the amount of 0.9 circulating plasma volume (CPV) with partial substitution of fresh frozen donor plasma achieved better results than in isolated dialysis [Matveeva I.B. et al., 2005]. Positive results also provide plasmapheresis before hemodialysis [Rabinovich V.I. et al., 2003].

The fevers caused by rickettsia of a tsutsugamushi (**rickettsiosis tsutsugamushi**) and "spotted" fever (**scrub typhus**), close to it, which are transmitted through stings of ticks are widespread in the countries of Southeast Asia. It is shown by symptoms of damages of nervous system (encephalitis, meningitis) and other organs with a serious endotoxemia [Rahi M. et al. 2015].

In recent years there were messages on a serious current of a number of the hemorrhagic fevers caused by the **Ebola viruses, Marburg, Dengue** who is followed by intoxication and severe shock with a lethality to 70-90% as treatment of these infectious diseases remains almost symptomatic [Leong A.S. et al., 2007]. Release from leukocytes of a number of cytokines (a tumor necrosis factor, interleukins 2, 6, 8) and other biologically active toxic substances which break permeability of vessels endothelium with development of toxic edema that is promoted development of shock and multiple organ insufficiency by is the cornerstone of pathogenesis of these complications. [Feldmann H. et al., 1996; Carr J.M. et al., 2003; Aleksandrowicz P. et al., 2008]. All these factors are justification of application and methods of a therapeutic

apheresis, in particular with use of a lectin-affinity plasmapheresis [Büttner S. et al., 2014].

Plagued the people, especially in the regions of tropical climate, is **malaria**. This concerns mainly the tropical its shape, called *Plasmodium falciparum*, which gives 98% of deaths from malaria [Shkurba A.V., Ovcharenko P.A., 2010]. Its crises are accompanied by severe endotoxemia with coma, acute renal and respiratory failure due to infectious-toxic shock. It particularly affected with children and pregnant women [Dhingra N. et al., 2010; Eilese T.P. et al., 2010].

Of course, by the main method of treatment of infectious diseases there is an aetiologic therapy – antibiotics, however not always they are rather effective. Therefore hemosorption which, besides an effective detoxification, provides also capture of microbes from the proceeding blood with prevention of their return to an organism considerably can give help. Nevertheless, only the decontamination and a detoxification isn't able to restore the immune potential of the patient yet. If the organism isn't able to resist to an infection, no antibiotics will help it.

And here comes to the forefront plasma **exchange which** besides removal of all pathological and toxic connections rather effectively restores immune system due to completion of the deleted volume by donor fresh frozen plasma. It contributes to more effective protection and recovery more rapid and full recovery.

And such tactics of carrying out primary detoxification and decontamination by means of hemosorption with the subsequent plasma exchange is represented to the most justified.

Supportive role played by the methods of indirect electrochemical oxidation and ozonation of blood, potentiating detoxification, and photo-hemotherapy (UV and laser irradiation of blood) having immunostimulatory effect. In general, significantly reduced consumption of antibiotics and other expensive medications, the period when the patients in intensive care units, the total duration of treatment, reduced mortality.

Danger is constituted also by various **poisonings**. They are very diverse in nature and exogenous toxic substances, the mechanisms of their effects on various tissues and organs, and processes for their entry into the body – inhalation, with water or food, through the skin. This may occur the various lesions of the area of the entrance gate – burns mucosa of the upper respiratory tract and respiratory parenchyma with inhalation

injury, burns of the mucous membranes of the mouth, esophagus and gastrointestinal tract with oral poisoning, chemical burns of the skin for transcutaneous way of toxic substances (TS).

Nevertheless, drought and significant common disorders of homeostasis due to direct toxic effects of penetrating TS and secondary metabolic disorders depending on the mechanisms of the striking effects of TS.

Upon the occurrence of hemolysis caused by **poisonous mushrooms**, a sharp increase in the concentration of free hemoglobin to the blockade of renal function. The most common is a disruption of lipid peroxidation with to the accumulation of toxic products and the suppression of the antioxidant system, decline in α -tocopherol, ceruloplasmin, superoxide dismutase, increased activity of the proteolytic enzymes, particularly peptidases, followed by increasing the level of middle weight molecular oligopeptides with the presence of free radicals in their structures. The appearance of circulating toxic products violates membrane potentials with excitation platelet aggregation, that contributes to the release of histamine and serotonin, which triggers a further cascade of DIC. Endotoxemia is accompanied by secondary toxic immunosuppression.

In some cases, there is a selective hepato-, nephro- or neurotrophic effects is more likely, especially in the terminal phase of the disorder develops multiorgan failure with a number of vicious circles, when the damage of hepatocytes further interferes with the natural detoxification, and the lesion of the glomerular or tubular kidney devices slows down as the primary damaging agent and the secondary products of disturbed metabolism.

In practically all cases of poisoning application therapeutic apheresis pathogenetic justified, and plasmapheresis in such cases is the most versatile method, even in cases when using dialysis can be derived low molecular weight TS (acetic acid, phenol), but rapidly advancing metabolic disorder with accumulation of medium- and large-molecular toxic substances which by dialysis impossible to remove. Severe organ disorders while contributing to the formation of products of "lethal synthesis", even more toxic than the primary xenobiotics.

With the help of high-volume plasmapheresis with replacement removed volume of donation fresh frozen plasma 1:1 managed to stop and extremely severe poisoning *pale*

toadstool with hepatic coma [Jander S., Bischoff J., 2000]. M.Valbonesi earlier (1986) also reported on the effectiveness of massive plasmapheresis with removal of up to 3 liters of plasma in patients with *pale toadstool* poisoning. Required for the course 4-7 such sessions, which reduced mortality by 15% compared with 80% in patients who carried only dialysis and transfusion therapy. Using therapeutic apheresis is most effective in the first 48 hours after mushroom poisoning. Sometimes removal up to eight liters of plasma for adequate decrease in levels of ammonia, urea and amino acids and knocking over of a hepatic coma is required. [Clemmesen J.O. et al., 2001].

Severe intoxication with cardiogenic shock, lungs toxic edema, brain damages and multiple organ insufficiency with a deadly outcome comes after **scorpions stings** [Bahloul M. et al., 2010; Petricevich V.L., 2010]. All this does shown and a plasma exchange also [Schwartz J. et al. 2013].

No less serious consequences occur after **snakebite** with development of microangiopathic haemolytic anemia and thrombocytopenia. Thus, when viper venom poisoning develop severe endotoxemia with increased levels of leukocyte index of intoxication (LII) to 3.78 standard units, level of middlemolecular oligopeptids ("average molecules") to 0.49 standard units (instead of be normal 0.24), ALT to 0.97 mmol/L, creatinine 129 mcmol/L, which was significantly higher than in healthy donors ($p < 0,001$). Application plasmapheresis could substantially reduce both general and local manifestations of poisoning compared with the control group, and reduce the overall length of stay in the hospital an average of 7.2 days [Pantanowitz L., Andrzejewski C., 2006; Yildirim C. et al., 2006; Moujahid A. et al., 2009].

For the American continent it is characteristic **Chagas' disease** - the chronic disease of heart which affected over 16 million people of the American continent and resulting from infection with the protozoa parasite of ***Trypanosoma cruzi***. After an acute phase of the illness which is shown esophageal bleedings often in 20-30 years damages of a gullet (dilatation), intestines (megacolon) and hearts with development of an inflammatory cardiomyopathy and serious dilatation of the heart cavities, congestive heart failure and a lethal outcome come to light. At histologic research the diffusion myocarditis with a degeneration of cardiomyocytes which is combined with fibrosis, a mononuclear infiltration and damage of elements of the cardiac conduction system in the absence of parasites comes to light [Mirkin G.A. et al., 1997].

These data specify on a high probability of autoimmune pathogenesis of this illness. Autoantibodies influence a G-protein of the myocardium receptors, such as β -adrenoreceptor and M2-acetylcholine receptor. There are signs of structural (anti-gene) proximity of an immunoprepotent ribosomal protein of this parasite and β_1 -adrenoreceptor that points to a possible cross molecular mimicry of these two proteins that forces the antibodies which are naturally developed against this parasite to react further and also with structures of own tissues of a cardiac muscle [Elies R. et al., 1996].

Thus, besides a myocardium, the antibodies developed against *T. cruzi* anti-genes cross react with anti-genes of an endothelium, of a brain and cerebellum neurons, peripheral nerves. It means that such "autoantibodies" actually have the heterogeneous nature, but react from autoantigens owing to proximity of anti-gene structure of a parasite and the host. Thus usual "threefold" therapy (azathioprine, prednisolone and cyclosporine) is capable to reactivate this chronic parasitic infection [Brenner Z., Gazzinelli R.T. 1997]. Therefore there are all indications for carrying out a plasma exchange for such patients.

It is necessary to consider that this parasite can be transferred both from mother to a fetus, and at hemotransfusions from the infected donors. And, even in not endemic regions of Ecuador and Bolivia about 1/4 donors are positive on existence of *T. cruzi*. This parasite can be very long in blood of the person, irrespective of his clinical state especially as the majority of the infected – the asymptomatic and can appear in the donors. The incubatory period of an illness lasts till 114 (!) days.

Can ache with such illness as tourists at visit of the countries located between 40⁰ Northern latitudes (Texas) and 43⁰ Southern latitudes (Argentina), and emigrants from these regions.

Considering autoimmune character against an endotoxemia the plasma exchange can be also used in the treatment of this serious pathology.

It must be admit that at the present stage, these questions do not have considerable controversy and debate, and only weak of the material base and the lack of trained professionals holding back wider adoption of methods of extracorporeal detoxification, immune and apheresis therapy in the practice of infectious medical institutions. Such task can be quite solved by means of simple and safe methods of a membrane plasma exchange on the portable device "Hemofenix" of the Russian company "Trekpor

Technology". It is promoted also by the small volume of filling, and their one-needle connection to any peripheral veins, including at small children [Voinov V.A., 2015]. [

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