Plasmapheresis for critically ill patients
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The book provides pathogenetic substantiation of efferent therapy and indications to it in various types of acute diseases and critical states. There are shown advantages of membrane plasmapheresis.

The book is intended for both, specialists in efferent therapy, resuscitation and doctors of other specialties.

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PREFACE

The reason for writing this book became an increasing conviction that in a variety of acute diseases with the development of multiple organ failure, the main causes of severe conditions and failures is endotoxicosis - the accumulation of various toxic products, without the removal of which neither a body, nor a surgery, nor the most effective medication and intensive care measures can lead to a cure.

And for many years in all these diseases, different in many respects, there are applied methods of efferent therapy based on removal from the body of what the organism cannot remove itself (kidneys cannot remove such large molecules, liver cannot destroy them).

However, unfortunately, far not all experts share this opinion and the author's main objective was to justify the need in this efferent therapy for various acute diseases and their complications.
LEGEND

ARF – Acute renal failure
BAS – biologically active substances.
DIC – disseminated intravascular coagulation.
AR – artificial respiration.
CPV – circulating plasma volume.
ECMO – extracorporeal membrane oxygenation.
LII – leucocytis index of intoxication.
MWM – middle weight molecules.
RDS – respiratory distress syndrome.
UBI – ultraviolet blood irradiation.

FiO₂ – concentration of oxygen in inspired mixture.
ABS – acid-base status
Ht – hematocrite (blood cells volume).
Ig – immunoglobulins.
IL – interleukins.
PaO₂ – arterial oxygen tension.
TNF-α – tumor necrosis factor - α.
INTRODUCTION

Efferent therapy is intended to eliminate from the organism various pathological products (the Latin efferens – elimination). In the past, rather popular was such a form of efferent therapy as bloodletting which apart from eliminating excessive circulating blood volume (CBV) released the organism from toxic elements. Even barbers were allowed to perform it. However, even in hands of experienced doctors this method was not deprived of hazards, so much the more the history knows the cases of failures of such procedure.

More safe method of efferent therapy is the removal of not the whole blood, but of its liquid part – plasma, components of which are the main carriers of pathological products in the organism, what’s more, it is restored much quicker than blood formed elements. This particular method is called plasmapheresis (from the Greek πλάσμα - plasma, liquid part of blood, and ἀφαίρεσις - apheresis, taking away). In this context "apheiresis" is from the Greek “removal” either.

Hippocrates himself wrote that “medicine is addition and withdrawal. Withdrawal of everything that is superfluous; addition of the missing. And the one, who does this best, is the best doctor”.

Nevertheless, the most popular methods of contemporary medicine are intended mainly to introduce into the organism of various drug preparations that are far from being harmless, but the number of which is continuously growing. Development of efferent therapy methods was hindered by lack of simple, cheap and accessible devices, and only during the last decade successes of membrane technology allowed to draw them nearer to the wide medical practice. What contributed most to it in Russia was creation of plasmafilter “ROSA” and device for membrane plasmapheresis “HEMOFENIX” developed by the Russian company “TRACKPORE TECHNOLOGY Corporation” and produced in Dubna, Moscow region.

The work aims to give more complete substantiation of efferent therapy indications in various acute diseases and critically conditions based on own experience and modern literature reports.
INTERNAL ENVIRONMENT OF THE HUMAN AND MECHANISMS OF ITS REGULATIONS

Human, like any biological entity, is in constant contact and interaction with the environment. Life is a constant process of metabolism both within the body, and with environment, absorption of oxygen and release of carbon dioxide, water and food intake and excretion of end products of metabolism. The very existence of the organism depends on the ability of constancy maintaining within certain limits of its internal environment.

During thousands of years of evolution there were perfected mechanisms of autoregulation of internal environment – homeostasis and protection against aggressive influences both from outside, and from poisonous and toxic substances, and microbial-viral contamination. But during the process of own metabolism as well, there are formed relatively toxic intermediate and final products of metabolism, which are subject to slow inactivation or removal. Therefore, formed a complex and multi-stage system of protection and correction of the internal environment. It consists of three main components:

1. Microsomal monooxygenase system of liver detoxification.
2. Immune system
3. Excretory system.

Hundreds of thousands of foreign compounds – xenobiotics – always get to the body from outside. The main liposoluble toxic substances undergo biotransformation during the process of digestion in intestine, from which by portal vein they can not bypass liver, where due to oxidation and enzymatic processes they finally convert into non-toxic water-soluble compounds, which are further metabolized in all organs and tissues.

Liver is a barrier not only for exogenous, but also for endogenous toxic compounds, constantly arising during the process of metabolism – synthesis of some and decay of other substances: lactate and pyruvate, urea and creatinine, ammonia and fatty acids, aromatic amino acids, alcohols and aldehydes, phenols and ketones, products of proteolysis and hydrolysis, activity of automicroflora and viruses, etc.

Immune system, in its turn, consists of three components: the central organs (thymus and bone marrow), lymphoid structures scattered over the body (spleen, lymph nodes), and immunocompetent cells.
There are the following parts of the immune system: recognition of foreign substances – antigens, phagocytosis, a cooperative function of T-lymphocytes and antibody production, interaction of antibodies with antigen and of complement with immunoglobulins and target cells. There are physical and chemical processes occurring: reception, immune adhesion and adsorption.

Interaction of antibodies with antigen is an adsorption process of forming the **immune complex** "antigen + antibody + complement". It is retained in the lymphoid tissue, phagocytized and degraded by lysosomal enzymes. Natural serum factors – opsonins – promote adherence of microorganisms, dead cells and their fragments ("detritus") to the plasma membrane of phagocytes (monocytes, neutrophils), increase the velocity of phagocytosis. It should be borne in mind that in case of depletion or absence of opsonins of complement, even normal phagocyte is not capable of capturing the bacteria, so defects in humoral immunity entails failure and cell-phagocytic defense mechanism.

But humoral immunity depends on the cell immunity as well, since T-cells are required for both, start of antibody forming by B-lymphocytes, and regulation of this process. In particular, T-helper cells (CD4) stimulate production of antibodies, and T-suppressor (CD8) inhibit this process, and, depending on the relations between the two subclasses (CD4/CD8), there are possible hyperimmune reactions and immunosuppression.

The task of the immune system also includes a struggle not only with food of foreign origin, but also with those arising within the body, including ever-emerging abnormal cells, which include tumor ones. Here also works a mechanism of a "friend or foe" reaction, and own cell with anomalous properties is destroyed along with the foreign ones by natural killer cells (T-killers) and other macrophages.

All final products of own metabolism and degradation of foreign substances, require removal from the body. The structure of **excretory system** consists of four components: kidneys, gastrointestinal tract, lungs, sweat and sebaceous glands of skin.

**Kidneys** remove water (1.5-2 liters a day) and dissolved urea, creatinine, potassium, sodium, chloride, calcium, magnesium, sulfates, phosphates. In addition, kidneys eliminate water-soluble products of biotransformation xenobiotics, products of proteolysis of immune complexes, remains of bacteria, viruses, protozoa, fungi digested by phagocytes, and substances spontaneously transformed into foreign substances.

**Gastrointestinal tract** eliminates lipids, cholesterol, bile acids, steroids, bilirubin, water, food debris, nonviable microbial body unabsorbed xenobiotics.
Through **lungs** there are removed carbon dioxide, water, volatile xenobiotics (ethanol, ether, etc.).

Sweat and sebaceous glands of **skin** derive water (400-600 ml), sodium, potassium, calcium, magnesium, phosphorus, chloride. Also urea, creatinine in case of uremia; in diabetes – glucose; in hepatic failure – ammonia, bile acids; in poisonings – mercury, arsenic, iron, iodine, bromine, quinine, benzoic acid, succinic and hippuricacid, salicylates, salol, antipyrine, methylene blue, etc.

**Mechanisms of homeostasis disorders**

In addition to the direct toxic effects of a number of xenobiotics, perversions of metabolic processes occur in the body. For example, penetration of oxidants stimulates lipid peroxidation with depletion, and then depression of antioxidant defense system. Final products of peroxidation, as malondialdehyde, diene conjugates, Schiff bases are accumulated. Increase of concentration of these natural metabolites leads to disorders and other metabolic processes, in particular, to excitation of proteolysis.

Another big disorder of homeostasis occurs in certain diseases. Thus, in acute inflammatory processes an important role play mediators of inflammatory with increase of kininogenase-kinin cascade products in blood – biogenic amines (serotonin, histamine, kallikrein) contributing to worsening of shock-producing reactions.

Upcoming biochemical disorders of internal environment can not affect the protection system – organs of detoxification, immunity, excretion. Developing "**toxic press**" causes a cascade of subsequent disorders with the emergence of a number of vicious circles that the body itself is no longer able to break, even with the help of various drug therapies.

Traditional approaches to treatment in most cases have symptomatic nature, such as the use of antibiotics for infections. If kidneys are not able to eliminate some products, then diuretics are not able to restore this function.

Without liquidating the reasons of depression or distortion of immune responses it is difficult to rely on a persistent immune correction. Without sanation of internal environment, excretion of pathological products, restoration of the normal course of metabolic processes, including lipid peroxidation and proteolysis, i.e., without liquidation of the "toxic press" on immunity, it is difficult to count on its recovery with only medical stimulation, without which it is impossible to achieve a breakthrough in the disease
course. Excretion of abnormal substances and sanitation of the internal environment are the aims of a variety of efferent therapy methods.

It should be noted that the concept of "pathological products" presupposes not so much toxic substances of exogenous or endogenous origin, as autoantibodies, immune complexes and other practical natural metabolites whose concentration exceeds physiological limits, which has pathological effects on organs and body systems.

**Methods of efferent therapy**

There are two groups of such methods. One of them is based on the possibility of applying sorption methods of fixation of various substances circulating in blood, and their subsequent removal. Another group includes methods of removing harmful substances together with a part of the blood – plasma.

**Hemodialysis** is also one of efferent therapy types. Clinical indications to it are limited mainly to acute and chronic nephropathy and some kinds of poisoning [Gotloib L., 1996]. These issues were rather fully described in a special literature and thus not included in the aims of this work.

In the intensive therapy practice more popular are methods of **hemofiltration** – **hemodiafiltration and ultrafiltration**. They are based on removal of liquid part of blood except for proteins, what makes them close to hemodialysis, but water exudation mechanism is based on filtration through microporous membranes. In this mode, can operate both conventional dialyzers and special hemofilters that allow to perform relatively long sessions for up to 180 hours with removal of up to 20-40 liters of liquid a day. Such intensive removal of the liquid needs special polyionic and buffer substitute solutions under the control of acid-base balance and ionogram.

**Sorption** methods are based on such peculiarity of many harmful products, as presence of the charge in these molecules or free radicals in their structure that in contact with the sorbent, consisting of activated carbon or other surface structures (sometimes coated with enzymes or ion exchange resins), are able to be adsorbed to the latter. Transmission of blood through the columns with sorbents is called **hemosorption** (hemocarboperfusion) [Ostapenko V.A., 1995].

It should be noted that many natural metabolites – protein molecules, lipids, mucopolysaccharides – have “closed” molecular structures electrically and, therefore, biologically inert. That is why “normal” metabolites can contact with active sorbents – they easily pass them by and remain in circulation, thus minimizing the possible harmful
effects of the procedure. Despite the common alienation of specialists, such nonspecific hemosorption still finds its application in the treatment of patients with sepsis, allergic and autoimmune diseases.

It is possible to apply sorption method without removal of pathological products and without elimination from the organism of any internal environment elements. This is an enterosorption. There is used a process of physiological filtration and reabsorption of liquid from the bloodstream into the intestine glimpse by its villi. The products that were removed with the liquid part of blood contact with enterosorbert taken beforehand, fix on it and together with it are removed from the body. Considering that the intestinal villi are able to pass all of the ingredients, the molecular weight of which is lower than the mass of albumin, and toxic substances at their core are of medium-molecular mass, the effectiveness of enterosorption in eliminating endotoxicosis becomes clear. The advantage of this method is the possibility of its use in ambulatory (home) conditions, although its efficiency yields to a direct adsorption of these substances directly from the blood flowing through the column during hemosorption [Nikolaev V.G. et al, 2005].

However far not all substances, subject to elimination from the organism, can be captured and fixed on sorbents. Electro-chemically inert molecules are incapable of adhesion and remain in circulation, which makes hemosorption procedure inadequate. In such cases the elimination effect of such substances can be obtained during plasmapheresis, when some part of plasma is completely removed together with all the pathological products that were there.

Removed volume of plasma is completed with plasma-substituting solutions, albumin and donor plasma. In the latter case, especially when the removed plasma is completely substituted with donor plasma, the operation is called plasma exchange. Unlike hemosorption, plasmapheresis has more or less universal character, when all the pathological elements are removed irrespective of presence and amount of electrostatic charge of their molecules.

There are two main methods of plasmapheresis – gravitational and filtrational. The first one is performed by centrifugation of blood with constant or intermittent flow in special devices produced by Gambro, Fresenius, Cobe, Dideco, Terumo or in bags in ordinary centrifuges.

The second method is based on blood filtration in special plasma filters. As a rule, there are produced filters, where filtration if performed through hollow porous fibers. In Russia there has been organised production of plasma filters PFM-800 containing flat
hollow “track” porous membranes (“PLASMOFILTER”, Saint-Petersburg). In 2001 appeared a filter of new generation PFM-TT “Rosa”, developed by “TRACKPORE TECHNOLOGY Corporation” and produced in Dubna, Moscow region. Description of peculiarities of the latter as well as different techniques of its application will be detailed below in the conclusion of the work.

In any of these methods after plasma removal, concentrated cell mass of blood (“erythromass”) is diluted with sodium chloride isotonic solution or other plasma substitute and returned to a patient. During one session it is possible to remove from 1/3 to ½ of circulating plasma volume (CPV). In case of donor plasma or albumine substitution, up to 1 or 2 CPV can be removed [Gurevich K.J. at al., 1993; Sokolov A.A., Bel’skich 2003].

CPV of an adult person with an average weight is 2.0–2.5 l. It is easy enough to calculate knowing the circulating blood volume (CBV), which makes about 7% from body weight and hematocrit index (Ht). Then there is elementary calculation:

\[ \text{CPV} = \text{CBV} - \frac{\text{Ht} \times \text{CBV}}{100} \]

Where – hematocrit index is percentage, and circulating blood and plasma volume – in milliliters.

If hematocrit was not measured directly, then it can be roughly calculated from the number of erythrocytes, which multiplied by 10 approximately corresponds to hematocrit (3,6\(\times\)10^{12}/l erythrocytes correspond to hematocrit 36%), or from hemoglobin content divided into three (hemoglobin 120 g/l - approximately 40% hematocrit).

After plasmapheresis session a significant decrease in the concentration of pathological products can be observed, but after a few hours their content in the blood is close to the original level. This suggests that substances, which before had been in the interstitium, or even in the cells, penetrated to the bloodstream. Subsequent sessions of plasmapheresis promote removal of these substances, which leads to a more complete sanitation of the whole internal environment, given that most of the harmful products are in extravascular space. It should be borne in mind that there is a “moving equilibrium” of concentrations of various substances in intracellular, extracellular (interstitial) and intravascular spaces of the organism. Change of their content in one of these spaces (in this case – intravascular) leads to redistribution in the others.
More selective methods of plasmapheresis are also used, when received plasma is subjected to cooling, which promotes the precipitation of some proteins and immune complexes, lipoproteins and triglycerides, fibrinogen, and other "acute phase" proteins, which in the future (after thawing) can be removed again by centrifugation or by sorption, and the remaining components of the plasma can be returned to the patient.

This method is called "cryoprecipitation", "cryosorption" or "cryosorption modification of autoplasma". Cold precipitation is enhanced in the presence of heparin, therefore one of such methods is known as heparin-induced extracorporeal precipitation of cholesterol (Heparin-induced extracorporeal LDL precipitation - HELP-apheresis. However, in the Technical Manual of the American Association of Blood Banks (2000) it is emphasized that by means of adsorption or cryopheresis it is possible to remove only a part of the pathological component, so the expected efficiency of these methods is lower than of those for which plasma is removed entirely.

Another method of selective plasmapheresis is cascade plasmafiltration when plasma obtained with one of the methods re-passes through a special microporous filter that passes only low molecular weight proteins (albumins) and holds those with high molecular weight, including immunoglobulins and atherogenic lipoproteins [Valbonesi M. et al., 2001; Hanafusa N. et al., 2006]. For the first time cascade plasmafiltration was performed by T. Agishi et al. in 1980 [Agishi T. et al., 2000]. As a secondary cascade plasmafilters there are used Albusave (Dideco, Italy), EVA-Flux EVAL 2-5A (Kawasumi, Japan), EC-20W (Asahi, Japan), Kuraray Evaflux 4 (Kuraray, Japan), etc.

Nevertheless, despite its importance, efferent therapy intended to remove pathological products of the internal environment, is only the first step in correcting its violations. The second one is elimination of secondary effects of these disorders – restoration of natural protective systems, mainly immunity.

In this book we use somewhat expansive notion of efferent therapy, including in it not only the removal of harmful substances from the body, but other methods of correcting defects of internal environment by physico-chemical influence on its individual components (blood, plasma, lymph) outside the body (extracorporally), or even inside it.

The basis of extracorporeal methods of immune correction is photo-hemotherapy (blood photomodification) – blood irradiation with ultraviolet or laser beams. There are many reports of favorable effects of such therapy: in patients with immunosuppression effect of immune stimulation is revealed, and with various allergies
– immune correction, that is, reducing pathological allergic reactions. In patients with inflammatory diseases of lungs after ultraviolet irradiation of blood electron microscopy indicates restoration of specific intracellular organelles in neutrophil leukocytes, suggesting an increase of their phagocytic ability. Also increases the number of immunoglobulins, T- and B-lymphocytes, reduces leukocytic index of intoxication (LII) [Nazarov I.P., Vinnik Y.S., 2002].

Among methods of laser irradiation of blood the most common is a helium-neon (He-Ne) laser as a light source of red light ($\lambda = 0.633 \, \mu\text{m}$). In case of coincidence of the enzymes absorption spectrum in a cell or in its membrane with energy spectrum of laser radiation, they are activated. In particular, catalase is activated, which has the same spectrum (0.633 $\mu\text{m}$), as He-Ne laser. Copper-containing redox enzymes – cytochrome oxidase and ceruloplasmin – may be acceptors. Activation of these enzymes is enhanced in the presence of singlet oxygen, which emphasizes the combination of this method with addition of substances containing free oxygen. It is possible a selective absorption of red quanta by oxygen with its transition to the singlet state. In such cases, it is justified to add substances containing singlet oxygen, for example – sodium hypochlorite.

Enzymes, such as superoxide dismutase, lactate dehydrogenase, phosphatase, can be acceptors of such irradiation. The red light of He-Ne laser influences hemoglobin molecules with decrease of its affinity for oxygen, which increases its impaction on tissues in hypoxia. This irradiation has a favorable effect on the lipid composition of erythrocyte membranes, normalizing their aggregation properties, deformability, which improves rheological properties and oxygen-transport function of blood.

When combined with efferent therapy, it is always possible to use extracorporeal circuit of perfusion and to perform more dosing irradiation. Eases the situation a good permeability for laser beams of the walls of PVC blood lines. A particular area of such tube can be placed inside a mirror sphere in which the tangential beam creates the effect of "inner lights shining" and irradiation of blood passing from all directions, which makes it possible to dispense irradiation with regard to the speed of blood flow and body weight. Combined application of laser irradiation of blood with hemosorption and plasmapheresis significantly potentiates their immuno- and rheologic impact, significantly increases efficacy of treating.

External irradiation of separate parts of the skin with He-Ne laser is also possible, but penetration of these rays is limited to only a few millimeters, which allows to irradiate superficial wounds or trophic ulcers. More deeply (up to 8 cm) penetrates radiation of
Infrared lasers with emission spectrum of 0.89 µm, which allows to use them in irradiation of both superficial large blood vessels and some of internal organs (liver, kidneys, heart, joints).

But in any case, plasmapheresis is associated with a temporary, renewable, but still lost of certain part of immunoglobulins, complement, opsonins, which, undoubtedly, at some time weakens immune protection capability of a patient. Thus, almost every operation of plasmapheresis (as well as hemosorption) must be accompanied by a quantum immunocorrection.

On the other hand, in almost all cases when quantum photo-hemotherapy is performed for immunocorrection, it is meaningless without parallel efferent therapy. This also can be said about different types of drug immunomodulation – without efferent therapy its effect will not be stable and long enough.

Efferent therapy can also be combined with methods of "oxidative detoxification" – low-flow membrane oxygenation and indirect electrochemical oxidation and ozonation of blood.

For the electrochemical oxidation it is used effect of electrolytic decomposition of usual isotonic sodium chloride solution with the device EDO-4 with formation of the above sodium hypochlorite (NaClO). Active radical ("singlet oxygen") of the latter in addition to bactericidal activity has the ability to rapidly oxidize hydrophobic toxic substances, such as bilirubin, creatinine, urea, fatty acids and other substances in the blood, which potentiates the detoxication process. Pre-treatment of hemosorbents with sodium hypochlorite increases their sorption capacity.

For ozonation of blood most commonly it’s used ozonation of isotonic solutions of sodium chloride with subsequent intravenous infusion. In such ozonization of blood there are reached effects of immunomodulatory, anti-inflammatory, anti-allergic. Decrease of concentrations of LDL, triglycerides, and glucose is also possible. Effect on the immune system manifests itself by activation of lymphocytes and macrophages with increased production of cytokines (interleukin-2), γ-interferon, β2-microglobulin. Apart from that, in introduction of ozonated solutions there is observed an effect of microcirculation improvement.
PARTICULAR ISSUES OF EFFERENT THERAPY
OF SOME CRITICALLY ILLNESSES

Respiratory distress syndrome

Acute respiratory damages of lung parenchyma are frequent and serious complications in a number of diseases. First of all of it is referred to viral and bacterial pneumonia, which sometimes has a cacoethic course and is accompanied by massive, sometimes total, bilateral damages of lung parenchyma with severe, hard correctable respiratory failure, which for several days, sometimes hours, can lead to death. Secondary to this there can develop destructive processes and even gangrene of the lungs.

The next group consists of acute lung damage, combined by the term "shock lung", developing in patients with severe trauma, who underwent surgery, including cardiopulmonary bypass on open heart (postperfusion pulmonary syndrome), hemorrhagic, septic or anaphylactic shock, massive blood transfusions (syndrome of "homologous blood"), leptospirosis and even tropical malaria with 57% lethality [Bhadade R.R. et al., 2011].

Apart from that, lungs are affected in various exogenous intoxications and poisonings. In obstetric practice lung damages develop in eclampsia, amniotic fluid embolism, disseminated intravascular coagulation (DIC) syndrome. Many types of endogenous intoxications, especially such as those developing in acute pancreatitis, are also accompanied by lung damage.

All these types of acute damages of respiratory lung parenchyma are usually combined by one term - respiratory distress syndrome (RDS).

In Western literature it was commonly referred to as "adult respiratory distress syndrome", or ARDS, where the first letter corresponds to the word “adult", which far not everyone was satisfied with, since a similar complication is characteristic for both adults and children. Therefore in 1994 the Conciliation Commission (Consensus) of scientists of European and American countries dealing with the problem had reviewed the terminology and, leaving the same initials ARDS, introduced a new term more close to the reality - acute respiratory distress syndrome, and the first letter in the abbreviation of the word has become “acute” [G.R. Bernard et al., 1994].

This book uses the term "respiratory distress syndrome" – RDS, because this syndrome can not be other than acute.
Considering such a large group of diseases associated with RDS, there are practically no compound statistical information about its frequency, although in 1980, in the U.S.A. there were cited the following data – about 150,000 patients with RDS a year. It is interesting that the materials of mentioned Conciliation Commission exactly the same figures are quoted for the United States for 1994. M.A. Matthay and R.L. Zemans (2011) describe approximately 200,000 critically ill patients with ARDS causes 40% mortality annually in the United States. Given the difficulties in treatment of this complication, accompanied by high mortality (10 to 90% depending on the severity of damage), this problem is extremely urgent.

Since in the solutions of Conciliation Commission, despite recognizing the essential role of endotoxemia in the genesis of this complication, was not mentioned the possibility of efferent therapy and detoxication in RDS, we have to give more detailed justification of such approach to its treatment and prevention.

Pathogenesis of respiratory distress syndrome

From the above list of diseases and pathological conditions accompanied by RDS, it is possible to make conclusion about polyetiology of this complication, however pathogenetic mechanisms are common for all types of RDS. They lie in the development of toxic interstitial and then alveolar pulmonary edema due to the cell membranes’ permeability failure on the basis of endotoxemia.

To prove this, in the Research Institute of Pulmonology, USSR Ministry of Health, there were conducted toxicity studies of blood in patients with acute pneumonia using the test of “protozoa survival time”. As the protozoa there were used tetrahymena. In the blood of healthy people (and animals) the survival time is about 20 minutes and, depending on the severity of condition of patients with acute pneumonia, this time was reduced to 10, 5 and even 2 minutes. However, this increase in toxicity of blood might have been only one of the consequences of acute pneumonia and have no independent significance in the further development of lung damage, which could have occurred simply from the progression of the basic pathological process in the same organ.

In clinical conditions the local pathological process and the accompanying intoxication can not be separated from each other, so it is impossible to identify those changes in the lungs, which are the direct consequence of the local pathological process, and those that arise from the impact of circulating toxic products. In one case, the process should be going in the direction of “alveolar epithelium – interstitium –
vascular endothelium”, in another – in the opposite direction, that is, from the blood. Only studies in the experiment could shed light on this question.

Our first experiments on rabbits with intratracheal administration of pathogenic (isolated from real patients) pneumococci culture gave quite amazing results – after only 5-10 minutes this pathogen was sown from blood and internal organs (liver, kidney, spleen), and the toxicity of blood increased to the same extent as in patients with acute pneumonia [Kostyanets E.Yu., 1992]. In all probability, the same bacteremia occurs in patients, and only the early start of antibiotic therapy does not allow to identify this phenomenon in more than 30% of them.

In histologic lung study of these animals there is revealed a picture of interstitial and alveolar edema against inflammation – expansion of interalveolar septa with infiltration of interstitium with lymphoid cells; in alveoli there was alveolar fluid rich with protein. Weight of the lungs increased by 32%.

When reproducing a similar level of endotoxemia with intravenous infusion of living or killed cultures of pneumococci there were also observed manifestations of pulmonary edema, such as those described above, but somewhat of smaller scale. Weight of the lungs increased by 25%.

It is interesting that both in intratracheal and intravenous insertion of the causative agent there was also observed a pattern of edema and extravascular fluid volume increase in liver, kidney, spleen [V.A.Voinov et al., 1991].

In experiments on dogs there were carried out thoracotomy and intravital contact lung biomicroscopy. Within 15 min after intravenous injection of both living and killed pneumococci cultures, on the surface of lungs there was noted an increase of interalveolar septa with accumulation of frothy fluid inside of alveoli. By the 30th minute, changes in the lung had been increasing, and had reached their maximum by the 180th minute.

For another series of experiments on dogs preliminarily there was received blood ultrafiltrate in its hemodiafiltration under pressure through the dialysis membrane from patients with severe lung damages and concomitant renal insufficiency. The liquid received was rich with medium molecular products. The powder resulting after lyophilization was redissolved for intravenous injection to dogs in such a way that the concentration of medium molecules in the blood of dogs corresponded to that of patients from which the ultrafiltrate had been obtained.

After intravenous injection of this solution in contact biomicroscopy there also may be noted the rapid development of interstitial and alveolar pulmonary edema on the
surface of the dogs’ lungs. Electron microscopy revealed a picture of destructive processes in the alveolar-capillary membrane, starting from the capillary endothelium. Similar results were obtained in a model of isolated perfused dogs’ lungs [Levanovich V.V. et al 1989]. A similar pattern of acute pulmonary damages on the basis of impaired vascular endothelial permeability was detected after adding endotoxins (LPS) of Gram-negative bacteria and Escherichia coli exotoxin [Schütte H. et al., 1997]. Moreover, it is exactly the lipopolysaccharide of Gram-negative enterobacteria and cytokines emitted by them (TNF-α) that play a key role in the development of septic shock, accompanied by refractory hypotension with violation of tissue perfusion and subsequent multiple organ failure [Zhang H. et al., 1997].

Experiments showed that in the development of respiratory lung parenchyma lesions arising against acute pneumonia, the leading role plays not so much the spread of the primary pathological process in the respiratory pathways, as endotoxemia due to release into the circulation of both living microbes and inflammation products leading to the permeability disorder in endothelial cell membranes with the release into the interstitium not only of liquid but also of protein. This was proved by a significant hypoproteinemia with the development of endotoxemia – a common protein in experimental animals reduced within an hour from 67.0 to 51.9 g/l, mainly due to albumin (albumin-globulin ratio decreased from 1.3 to 0.7). These observations confirm that the observed hypoproteinemia, reaching a protein level of 40 g/l, is also a consequence of proteins moving to interstitium through more porous membranes of capillary endothelium. This correlates with the increase of protein concentration in lymph also approaching the level of 40 g/l, instead of usual 20 g/l.

Thus, in patients with acute pneumonia, develops a dual type of lung disease - primary, depending on spread of pathogens in airways, and secondary, arising due to penetration of bacteria and inflammatory products from the primary site into the blood with the development of toxemia. Risk of lung parenchyma was no longer threatened by epithelium of respiratory tract, but by blood through from vascular endothelium [Voinov V.A., 2013].

Toxemia character is also multicomponent. Apart from actual bacterial toxins (for pneumococc it is hyaluronidase, neuraminidase), both living and dead microbial bodies, in the blood penetrate tissue decay products, inflammatory mediators, the whole complex of biologically active substances (BAS) – products of kallikrein-kinin cascade, histamine, serotonin, products of lipid and proteolysis peroxidation and metabolism of tissues (medium molecular oligopeptides), leucocyte decay (lysosomal enzymes).
With electron-microscopic studies in lung microvessels it was possible to detect evidence of previously described *marginal leukocyte position syndrome*, when leukocyte was observed in decay stage, adhered to endothelium, with lysosomal corpuscles fixed to the endothelium and outside leukocyte with significant perifocal zone of the vascular wall destruction.

All types of these toxic substances disturb the permeability of cell membranes, not only of lungs, but virtually of all other internal organs and tissue structure with their functional status failure and development of *multiple organ failure syndrome*. Although this condition is often characterized as RDS by the most manifest signs of respiratory failure and radiographically detectable changes, while disturbances of other organs are apparently not so striking, yet it is difficult to imagine an isolated RDS during normal operation of other organs. In septic shock with acute endotoxemia there may develop hemodynamic disorder manifested in a blood pressure fall, total peripheral vascular resistance reduction, decrease of cerebral blood flow and intensity of oxygen consumption of brain tissue [Pollard V. et al., 1997].

Moreover, there appears a series of *vicious circles*, when the toxic pulmonary edema and hypoxemia stimulate hypoxic disturbances in membrane permeability; renal irritation contributes to the additional retention of fluid (edema is stimulated) and slag (toxemia increases); liver damage with the suppression of its detoxication function also enhances toxemia; toxic *myocardioopathy* aggravates organ microcirculatory disorders, and toxic *encephalopathy* leads to brain disorders, while released neuropeptides stimulate *neurogenic* pulmonary edema. Exactly this "summation" of damages in multiple organ failure determines extremely high mortality rate – up to 80% [Gotloib L., 1996]. The syndrome of multiple organ failure reflects a biological disaster, type of biological suicide that occurs in a wide range of clinical situations.

Pulmonary capillary endothelium damages, in addition to the development of interstitial edema, also lead to the failure of microcirculation and mikrothrombosis, which leads to appearance of ischemic lung parenchyma foci and subsequent *destructions*. Alveolar edema prevents the oxygen access to the interstitium, which in the presence of local ischemia and anaerobic microflora leads to the lung *gangrene*.

Interstitial and alveolar toxic pulmonary edema blocks gas exchange at the alveoli level due to the expansion of aerohematic barrier (alveolar-capillary membrane). This leads to severe and hard correctable *parenchymatous respiratory failure*, a leading factor of *thanatogenesis*. 
Approximately the same mechanism of RDS development is in septic and burn shock, other types of endotoxemia [Eryuhin I.A., Shashkov B.V., 1995]. In traumatic shock a fat embolism significantly contributes to the general background of endotoxemia. However, there meant not so much the fact of penetrating to the circulation of free fat from tissue destruction areas (which, of course, takes place), as the failure of the lipid suspension state and formation of fatty globules in the vascular bed already. This activates lipase, and as a result of lipolysis there is sharp increase of free fatty acids and lysophosphatides concentration with pronounced membrane activity.

In severe injuries and, mainly, crushing syndrome, prolonged tissue ischemisation and autolysis development there are formed highly toxic products of tissue decay, myoglobin and free hemoglobin (due to hemolysis), which have the most damaging effects on their excretion ways – on parenchyma and kidney function, which often results in hemodialysis need.

Toxic products circulating in the blood have a damaging effect not only on the endothelium of blood vessels, but on the blood ingredients, mainly on the cells. Permeability disorder, mechanical and electrostatic properties of erythrocyte membranes contribute to their aggregation (sludge) and even greater disorder of blood rheology and microcirculation. Excitation of leukocyte membranes contributes to the increase of their adhesive properties and retention in microvessels (marginal leukocyte position syndrome). Platelet activation also enhances their adhesiveness, appearance of micro-aggregates that become like nuclei for subsequent formation of DIC cascade stimulating microthrombosis and bleeding.

Thus, RDS is a secondary toxic damage of respiratory parenchyma, occurring not only in lung diseases but also in a number of other pathological conditions that share common pathogenetic mechanisms. The main among them is toxic cell membrane permeability disorder.

Special studies conducted in the 70’s showed the activity disorder of surfactant in the development of shock lung. Surfactant reducing the surface tension in alveoli and thus ensuring their stability on the exhale, also reduces the hydrostatic pressure in pulmonary capillaries, preventing the extravasation of fluid from them [Perez-Gil J., Weaver T.E., 2010]. Thus, lack of surfactant leads to atelectasis as well as to pulmonary edema. The main active agent of surfactant is a phospholipid dipalmitil-
phosphatidyl choline, but there are protein components, it means that surfactant is a lipoprotein, synthesis of which occurs in alveolocytes type II.

There are several attempts to explain the decrease of surfactant activity. In particular, it is assumed that the fluid and protein entering alveoli in edema disrupt surfactant layer and wash it away. However, direct inhibition of surfactant is also possible under the influence of some toxic substances, among which are free fatty acids [Günter A. et al., 2001; Zasadzinski J.A. et al., 2010; Lu K.W. et al., 2011]. Histochemical studies have shown that as early as 2 hours after the hemorrhagic shock there occur changes of surface-active film of alveoli, its fragmentation.

In some experimental investigations there was also discovered surfactant inactivation after introduction of bacterial endotoxines [Davidson K.G. et al., 2002]. Status of lung surfactant system and reasons of its damages have been studied by us. For this there was worked out a method for direct measuring the surface tension by method of J. Clements (1957 For that 3 g of lung tissue was disintegrated by scissors and surfactant was extracted in 50 ml of isotonic sodium chloride solution. After 30 min exposition with constant intermixing the extract of lung tissue was placed in a special cell, the surface area of which could gradually decrease from 100% to 20%, making it possible to record the hysteresis loop of the surface tension, which was measured by a quartz plate retracting force on the Wilhelmy-Langmuir balance (A.F. Ovchinin). Of the highest information content was the surface tension in reduction of the cell area to 20% (according lung expiration), reflecting the maximum activity of surfactant in the extract, or "minimal surface tension" (normal - 2-6 dyn/cm).

And further the "minimal surface tension" we will denominate as simple “surface tension” marked as dyn/cm (m\Nm).

Surfactant activity was determined by measurement of surface tension of lung extracts, derived from 12 patients, who were dead after acute pneumonia and lung abscess or gangrene. Surface tension of pieces lung tissues of healthy dogs derived during thoracotomy was decided as normal surface tension. It was average 5.2±0.7 dyn/cm and in our patients it was average 20.29±1.6 dyn/cm. But in more detailed examination it was find that lung surfactant activity of patients showed a significant increase in the surface tension of extracts taken from the most altered parts of the lungs on the stage of their “hepatization” (27.37±1.48 dyn/cm to a maximum of 32 dyn/cm), while in areas with the aerial, suppression of surfactant was less pronounced (14.41±1.29 dyn/cm). This difference of surfactant activity in different parts of lungs of the same patient might have depended on its additional inhibition in the places, where in
toxic pulmonary edema the maximum yield of the toxic components of blood plasma in the alveoli took pace.

Possibility of direct inhibition of surfactant by some substances circulating in blood at first glance may seem unlikely, since the surfactant lining the alveoli inside is protected from exposure to these substances alveolo-capillary membrane. However, in RDS development, permeability of the membrane is disturbed, what allows to penetrate into the alveoli with edema fluid and these toxic substances. In such case, the direct contact with their surfactant is possible.

For clarification of reasons of surfactant activity disturbances at the absent of whole organism influences there were carried special experiments in vitro. There were added by 10 ml blood of healthy dogs (5), healthy people (5) and 10 patients with severe lung disease – acute pneumonia, abscesses and gangrene of lungs.

Initially, it was found that blood of healthy animals and people (donors) did not suppress the surfactant activity (tabl 1).

<table>
<thead>
<tr>
<th>№</th>
<th>Object of investigations</th>
<th>Initial level</th>
<th>After blood addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Healthy dogs</td>
<td>5.2±0.5</td>
<td>5.7±1.1</td>
</tr>
<tr>
<td>2</td>
<td>Healthy volunteers</td>
<td>4.9±0.7</td>
<td>5.4±0.9</td>
</tr>
<tr>
<td>3</td>
<td>Patients with RDS</td>
<td>5.2±0.7</td>
<td>25.08±3.76*</td>
</tr>
</tbody>
</table>

Note: mark * – difference from initial level is significant (P<0.05).

At the same time the blood of sick people caused inhibition of surfactant. Due to using extracts of pre-chopped lung tissue in these in vitro experiments, the suppression of surfactant in these cases depended not on a "disorganization" of surface-active layer of alveoli or mechanical surfactant flushing with edematous fluid, but on direct inhibition of surfactant activity by toxic substances of blood.

Thus, these studies have convinced us that in pathogenesis of acute pulmonary damages surfactant system disturbances play a secondary role, being not so much the cause as a consequence of these damages.
Clinic and diagnostics of respiratory distress syndrome

One of the most characteristic and early manifestation of RDS are dyspnea, cyanosis, and tachycardia. Auscultatorily are early marked hard, and then bronchial, breath due to increased sound conductivity of pulmonary stroma with interstitial edema. On later stages, breathing may be impaired or not even be present at all ("mute" or "silent lung"), especially in lowback parts. Rales are not abundant, mostly dry, although a crackling sound can be heard. Sputum is poor or may be absent unlike hemodynamic ("heart") pulmonary edema, which is characterized by copious amounts of foamy sputum.

In blood gas analysis the first sign is hypocapnia, then appears and increases hypoxemia and only in the terminal phase hypercapnia increases. It is characteristic of metabolic alkalosis.

X-ray pattern reflects the main stages in RDS development. Initial stage is characterized by signs of interstitial pulmonary edema: general strengthening of the pulmonary pattern over all parts by means of perivascular and peribronchial fluid accumulation. Unlike other organs, lungs are normally characterized by two ways of lymph outflow – to the center and to the periphery (in the direction of pleural cavity). Therefore, increase of lymph outflow toward the center leads to the increase of shade and loss of lung structural roots. Direction of lymph outflow to the periphery of lungs contributes to appearance of moderate excess fluid in pleural cavity and stressed interlobular boundaries.

In RDS progression and development of alveolar edema phase, first there appear small (a "blizzard" symptom), and then larger focal and confluent shadowing, mainly in lowback of lungs.

Approaching to the terminal phase is characterized by intense homogenous shading of lung tissue in the lower and middle sections, merging with shadows of heart and diaphragm (liver). Airiness retain only on the top of lungs.

Radiographically detectable signs of RDS can be completely balanced or dominate in any part, especially in cases of prior pneumonic foci, around which perifocal changes in lung tissue are more pronounced.

As noted above, RDS is accompanied by severe hypoproteinemia, which leads to decrease in oncotic pressure and hypovolemia with blood thickening, which contributes to microcirculatory disorders and labilizes central hemodynamics. Disorders of the latter and direct influence of toxic substances to kidneys are accompanied by decreased urine
output and positive water balance in general, hepatic dysfunctions reflect the moderate increase in concentration of bilirubin and transaminases.

Mild leukocytosis is possible, but often the total number of leukocytes is not excessive, with a slight shift to the left and relative decrease in the number of lymphocytes. Also falls the phagocytic activity of leukocytes. There is marked the toxic granulation of neutrophils.

One of the few methods of objectifying and quantifying the intoxication level is to determine the concentration of medium molecular oligopeptides of blood (level medium molecules). The most simple and affordable rapid test is in fact a method proposed by N.I. Gabrielian (1985), giving an integral characteristic of this indicator. The normal level of medium molecules is retained within 220-250 units. In moderate intoxication, this index rises to 350-400 units, in severe - to 500-600 units, with maximum increase to 900 - 1200 units, which reflects almost incurable state. More fully the nature of endotoxemia is identified with the method of determining medium molecules, proposed by M. Ya. Malakhova (1995). In recent years, to diagnose the severity of septic complications there has been determined the level of procalcitonin (normal – 0.1-0.5 ng/ml, 0.5-2.0 ng/ml – moderately excessive, 3.0-30.0 ng/ml – high, 100.0-1000.0 ng/ml – very high) [Shestenko O.P. et al, 2005].

One of the most precise criteria for RDS diagnostics are various methods for determining the volume of extravascular lung fluid (ELF). In vivo, in dynamics as well, there can be used various colorful, radionuclide techniques and thermodilution. Noteworthy are the results of such research, testifying that even after mild surgical procedures outside the chest cavity, there are signs of ELF increasing. It is also noted that even a twofold increase of ELF volume still could not be accompanied by changes determined clinically, radiologically, or laboratory (blood gases). When the first signs of RDS are observed, it means there is already the far gone disease process.

Taking into account these data, the true frequency of this complication can be questioned. It can be assumed that **RDS phenomenon is almost constant companion of many pathological conditions and diseases.** There should be referred not so much the frequency of RDS, as **the frequency of the particular RDS severity.** Probably this is the extreme view, but it is closer to the essence of the problem, than actually its complete negation in a wide range of diseases, because, admitting the fact of RDS, we can duly put the question of pathogenetic therapy.
Treatment of respiratory distress syndrome

Unfortunately, at present, RDS is not always diagnosed. In case of complications against viral and bacterial pneumonia, only the dynamics of the process spread in the lungs is recorded without proper pathogenesis evaluation of the observed changes in respiratory parenchyma. When RDS arises against severe injury and operative interventions, pancreatitis, septic and burn shock, there are often made such unconvincing diagnoses as "hypoventilation" and "hypostatic pneumonia".

Traditional approaches to the treatment are largely determined by the above diagnoses and therefore inadequate evaluation of the causes of this complication. Under influence of such diagnosis like “hypoventilation” they try excessive lungs overinflation during artificial lung ventilation with “positive end expiratory pressure” (PEEP).

Where the cause is only the inflammatory component of pathogenesis, the effort is aimed at providing antibacterial therapy, search for new, more powerful antibiotics of "super wide" action. It is believed that the process progression is associated only with low sensitivity of causative agents to antibiotics.

Of course, it would be unwise to reject the use of antibiotics in those cases where microbial flora is a major etiologic factor. Even with the development of RDS against injuries and major operations, microbial inflammation can be easily added to those changes in lungs, which occurred due to permeability failure in cell membranes and toxic pulmonary edema. Therefore, antibiotics should remain in complex treatment and prevention.

Similarly, it is necessary to use remedies to improve the resistance of organism (vitamins, immune-boosting drugs), cardiotonics, stabilizers of membranes, antioxidants, disaggregants.

However, any, even the most effective antibiotics, killing bacteria, are not able to eliminate their toxins, and microbial bodies themselves require a special system of elimination, but with reduced phagocytic activity they linger in the body and continue their harmful effects. The very fact of microbial infection activation suggests the weakening of the organism's defense system, its inability to cope with the pathological condition. One of the major reasons for the suppression of immune defense is the fact of initially transferred influenza or other respiratory viral infections, immunosuppression in patients weakened by previous chronic illnesses, intoxication. Among the latter,
significant are not only alcoholism and drug addiction traditionally considered in such cases, but consequences of a number of environmental, industrial, food factors, etc.

Many doubts are caused by the cases of using drugs and transfusion means improving the rheology of blood. Justification of this treatment appear quite convincing, as above mentioned hypoproteinemia reduces the oncotic blood pressure, that prevents necessary amount of liquid from keeping in the bloodstream, a natural consequence of which is hypovolemia, only partially compensated by increase in cardiac output during tachycardia. A logical tendency is to use transfusion therapy to restore oncotic pressure and CBV by colloid plasma substitutes and even albumin [Shoemaker W.C., Wo C.C., 1998].

When these solutions are retained by endothelium and remain in circulation for a long time, everything would go well in the norm, but in terms of increased porosity of the vessel wall, they "fall" to the interstitial space, increasing the oncotic pressure there, even more stimulating the passage of fluid from the bloodstream to tissues [Nazarov I.P., Vinnik Yu.S., 2002]. And it wasn't once, when transfusion tactics done with the best intentions and being quite justified, in just a day resulted in almost total lung hepatization, severe respiratory failure.

Even in absence of frank endotoxemia in patients undergone major surgery, with excessive positive water balance of more than 67 ml/kg of body weight within a day, there may develop severe pulmonary edema with a fatal outcome [Arieff A.I., 1999]. Extrapolating own clinical data to the nationwide (USA), the author believes that there can occur from 8,000 to 74,000 fatal cases a year from postoperative pulmonary edema.

In no doubt is oxygen therapy, i.e., by some means adding oxygen to the inspired air, since extension of the alveolar-capillary membrane in edema sharply reduces diffusion of oxygen through it, although carbon dioxide as a more soluble, still retains the ability of adequate elimination. However, hopes for recovery of gas exchange function in lungs by means of artificial lung ventilation (ALV) seem rather illusory, since the ventilation is really capable of correcting the ventilative respiratory insufficiency, but diffusion failures at the level of alveoli make its use in parenchymatous respiratory failure unsuccessful. Though resuscitators of Europe and America are still hoping to select some special ALV parameters, in particular by increasing pressure in the airways at the end of exhalation.

One must admit that maintaining pressure of 5-10 cm H_2O at some point can improve gas exchange by hyperinflation with not yet completely filled alveoli exudate.
However, special physiological studies have shown that not only isn't VELF reduced, but even increased because of higher porosity of hyperinflated alveolo-capillary membrane, increased filtration area and obstacles in lymph outflow from lung parenchyma with increase of intrathoracic pressure [Demling R.H. et al., 1975]. It is known that long-term artificial ventilation even in ventilative disorders stimulates fluid retention in lungs, inhibits diuresis, contributes to lung barotrauma [Kolesnichenko A.P., Gritsan A.I., 2000].

Apart from that, almost natural complication of prolonged ALV is pneumonia that develops not only as a result of microbial insemination of respiratory tract, but also in the development of systemic inflammatory response syndrome (septic shock) with the release of cytokines such as interleukins 6 and 8 (IL-6, IL- 8) and tumor necrosis factor alpha (TNF-α). At the same time it is noted that increase in their level occurs even 3-4 days prior to pneumonia development [Bouten M.J. et al., 1997; Ranieri V.M. et al., 1999]. Joining pneumonia against RDS is difficult to diagnose, because its symptoms such as leukocytosis, fever, and radiographically determined changes (infiltration of lungs), are already available in RDS without infection. On the other hand, endobronchial and pathomorphological studies suggest the presence of respiratory infection on 2-6 days, and pneumonia signs on 5-12 days of RDS development [Delclaux C. et al., 1997]. In addition, ALV leads to damage of tissues and other organs, in particular to apoptosis of epithelial cells of kidneys and small intestine, which enhances the manifestation of multiple organ failure even more [Iwai Y. et al., 2003].

Because of development of methods on producing synthetic or semi-synthetic surfactants, in recent years has increased interest in the possibility of their use in RDS treatment. However A.Anzueto et al. (1996) when analyzing the results of large randomized study of surfactant therapy effectiveness in 700 patients no effect on the survival rate, ALV duration and stay in the intensive care department or a state of physiological lung function was observed.

During many of more late investigations it was noticed only short-term effect of insertion exogenous surfactant [Spragg R.G. et al., 2004; Davidson W.J. et al, 2006; Bream-Rouwenhorst H.R. et al., 2008; Kesecioglu J., Haitsma J.J., 2006; Briel M. et al., 2010; Matthay M.A., Zemans R.L., 2011]. In particular A.V.Vlasenko et al. (2006) discovered, that surfactant use could reduce ALV duration and length of staying in the intensive care department, but there was no significant reduction in mortality rate (causes of deaths were sepsis and multi organ failure). And in Russia surfactant use in
Infants provided a more rapid decline of FiO$_2$ up to 40% and reduction of ALV length, but survival increase by 7 and 28 days wasn't achieved as well [Shalamov V.Y. et al, 1999].

Thus, no satisfactory results of use of surfactant, on the one hand, and achieving much better results in the application of methods of detoxification for RDS, on the other hand, suggests that the true cause of the fall of surfactant activity is its inhibition of toxic substances penetrating into the alveolus at toxic violation of vascular permeability. Thus introduced exogenous surfactant, as well as natural also falls under the effect of these toxic substances, and their activity ceases.

Using detoxification contributes to the elimination of porosity vascular pathogenically is more reasonable treatment of RDS, as after the termination proceeds into the alveolus of toxic substances in the coming hours restored reproduction of natural surfactant, which eliminates the need for its introduction of exogenous drugs.

This also applies to cases of RDS in premature infants who do have a deficiency of surfactant, but most often develops on RDS "adult" type – as toxic pulmonary edema as a result of entering the bloodstream of the fetus when the mother endotoxins disorders of pregnancy, which caused a premature birth. Therefore, such a newborn justified the use of detoxification – specially developed method syringe membrane plasmapheresis [Voinov V.A. et al., 1996], after which there is no need in the additional introduction of exogenous surfactant.

Thus, the results of the studies, confirming the toxic nature of the violations surfactant activity in acute pulmonary injuries, give reason to assume that the termination of admission to the alveolus of toxic substances from the blood by the methods of detoxification is more justified than the additional administration of exogenous surfactant.

In the seventies of the XX century these facts made some scientists refer to using extracorporeal gas exchange with the help of membrane oxygenators, which by then had been produced to improve the results of open heart surgery. In animal experiments it was possible and safe to maintain gas exchange for up to three weeks with the membrane oxygenator. This provided a basis for their use as supporting extracorporeal membrane oxygenation (ECMO) in acute parenchymatous respiratory failure.

The first results of RDS treatment with ECMO were quite encouraging. Indeed, immediately after connection of membrane oxygenators gas exchange was restored,
patients' condition stabilized. However, the inverse dynamics of considerable pathological changes in lungs were not noted. After the procedure, inflammatory and destructive processes progressed again. Favourable outcome could be reached only in 20-30%, mostly among children. In recent years, ECMO effectiveness has increased to 47-60% [Bartlett R.H. et al., 1996; Kolla S. et al., 1997; Fortenberry J.D., Paden M.L., 2006; Maclaren G., Butt W., 2007; Zabrocki L.A. et al., 2011].

GJ Peek et al. (1997) summed up the seven year experience in ECMO applying in 50 patients with RDS and the overall survivability of 66%. With the help of percutaneous cannulation it was possible to reach speeds of veno-venous perfusion of up to 120 (ml/kg)·min and provide extracorporeal gas exchange for an average of 207 hours. During this period the patient needed the transfer of up to 19 doses of blood, significant values of donor plasma, platelet concentrates, provision of parenteral nutrition, day and night surveillance and maintenance of highly skilled specialists, which required considerable financial expenses far exceeding $100,000. Use of ECMO for the treatment of neonatal respiratory distress also required not less than $50,000 [Roberts T.E., 1998]. Given such difficulties and complexity of ECMO operations, they are not widely known. However, extracorporeal membrane oxygenation has taken a definite place in treatment of RDS, recommended by mentioned Conciliation Commission.

In some cases there is used a method of extracorporeal CO₂ removal through membrane oxygenators, but own lungs are maintained in a state of functional rest, ensuring constant and almost oscillating flow of oxygen to maintain an adequate level of oxygenation [Morris A. et al., 1994; Falke K.J., 1997].

In recent years there have been describes attempts to use the full or partial liquid ventilation with perfluorocarbon with maintaining the normal mode of gas ventilation or ECMO, which have shown quite promising results in treating RDS, in both adults and neonates [Cox P.N. et al., 1997; Kolla S. et al., 1997; Yoxall C.W. et al., 1997; Davies M.W., Fraser J.F., 2004]. Using high ventilatory support against partial liquid ventilation has showed no advantages over the conventional volumetric ALV [Smith K.M. et al., 1997].

Nevertheless, conventional methods of intensive therapy are still most commonly used with different variants of lung ventilation. S. Vasilyev et al. (1995) summed up the experience of 25 centers in the USA and Europe, where there were 1426 patients with RDS. Everyone was performed artificial ventilation. If in the beginning of ALV with FiO₂ of 0.5 and more, there was no hypoxemia or hypercapnia, but survivability was 63.6%, if there was a significant hypoxemia and hypercapnia, survived 33.3% of patients. If there
was only insufficient acute respiratory distress, 40% of patients survived, with multiple organ dysfunction there were not more than 10% survivors.

It is possible to find information about financial expenses for conservative RDS treatment [Angus D.C. et al., 1996]. Average cost was $79.355 (for survivors - $83.437, for the dead - $ 71.073), which is not much less than in using ECMO. Given that annually in the U.S.A. RDS occurs in 126,000-159,000 patients (mortality - 30-60%), the total cost of treatment ranged from 9.6 to 12.7 billion dollars. In this case, therapy, which had reduced treatment cost for at least 1%, would have resulted in total saving of up to $100 million a year.

The presented analysis shows the complexity of RDS treatment issues, but also the almost complete absence of pathogenic approach to its therapy, which consists in ignoring the fact of endotoxic nature of lungs’ and other organs’ damage and, as a result, not using methods of detoxification, apart from a number of cases of hemofiltration against ECMO.

Our own initial attempts of extracorporeal membrane oxygenation in RDS did not yield the expected results because of inability to halt the progression of pathological processes in lungs and multiple organ failure, despite the correction of impaired gas exchange during surgery.

On the one hand, these failures and, on the other hand, results of experimental studies that showed the toxic nature of lungs’ and other organs’ damages, have convinced us of the need to use methods of detoxification. In these conditions only methods of direct blood detoxification can halt progression of the process, breaking various vicious circles.

**Detoxication methods in respiratory distress syndrome**

Proof toxic nature of RDS was the basis for its treatment tactics developed using various methods of detoxification – hemosorption and plasma exchange [Voinov V.A. et al., 2007]. Even when using the extracorporeal membrane oxygenation (ECMO), the main effect is the sorption column in perfusion circuit. At the same time, even against the background of almost total destruction of the lungs, after 8-10 hours of lungs airiness observed recovery, and their almost complete normalization was achieved after 24-36 hour. At the same time when using only one ECMO, but without detoxification, to achieve the same effect required two weeks. On the other hand, through detoxification,
without resorting to ECMO, and even without the introduction of surfactant, managed to reduce mortality in severe RDS from 74 to 31%.

Exactly the same positive effect gave the use of detoxification (membrane plasmapheresis), with respiratory distress syndrome, or RDS in neonates, including very preterm and weighing up to 700g, which is considered a deficiency of surfactant pathogenically mechanism of pulmonary lesions. At the same time without any major additional surfactant is also doing a few hours on X-ray examination showed regeneration of lung airiness.

In 1980-1990 Russia's most accessible and safe method of detoxification in RDS was **hemosorption** (hemocarboperfusion) using activated carbon of SKN, SUGS, VNIITU marks, etc. When passing up to 3-4 CBV through a column, many pathological products were completely eliminated, and even live bacteria were retained and fixed, which, for example, in infections caused by *Pseudomonas aeruginosa* is the only truly effective method of treatment, because antimicrobial therapy is inadequate. The level of medium molecules reduced as well as toxicity of blood in general (according to the survival time of protozoa), the general condition improved, changes in lungs underwent involution seen in X-ray study [Voinov V.A. et al, 1985, 1992].

Hemosorption was effective in destructive processes, and even in pulmonary gangrene. It is natural that areas of lungs subject to ichorization could not restore the structure, but perifocal changes and intoxication reduced, which allowed to prepare patients more quickly for the inevitable surgery that was easier tolerated [Levashev Yu.N. et al.,1989. Despite the remaining areas of gangrene, disappearance of quite intolerable smell of breath was surprising. This indicated that the smell of breath is formed not only in the respiratory tract, but mainly by penetration of pathological products from blood through aerohematic barrier. It means, this was the smell of the blood itself, reflecting the accumulation a large number of pathological decay products in it.

However, in advanced stages of RDS against frank parenchymatous respiratory failure that required artificial ventilation, hemosorption was no longer capable of changing the course of the pathological process. Instead of the expected decline, the level of medium molecules increased above the initial, apparently due to their leaching from depot and damaged tissues, improval of microcirculation and blood rheology. The clinical picture also showed increasing severity of multiple organ failure. In these conditions only **extracorporeal membrane oxygenation** (ECMO) at a speed
of 25-30% of blood flow cardiac output and up to two days made it possible to gain time, i.e., to maintain gas exchange at the lowest appropriate level and during this time to provide more active detoxification. Only this combination of a massive detoxication (up to three hemosorption sessions during a day) during ECMO made it possible to provide regression of organ lesions in extremely severe stages of RDS. Out of ten such incurable patients it was possible to save seven [Voinov V.A. et al, 1985, 1995; Lapshin V.N. et al., 1997].

It should be noted that, according to G.J. Peek et al. (1997), for RDS treatment with ECMO on the average there were needed **207 hours** and a lot of donor blood, plasma, platelet suspension and other drugs, which explained extremely high cost of such courses (over 100 000 dollars). But in our case, to relieve very severe RDS it took only **20-40 hours**. The difference in the tactics of treatment was the only one – together with ECMO we performed intensive **detoxification** with hemosorption, which is ignored in US and Western Europe.

It is necessary to emphasize once again that during ECMO true therapeutic effect was created by detoxication, which would have never been achieved with the most adequate and continuous membrane oxygenation that we reckoned upon earlier, and that is still recommended in isolation (without detoxication).

Nevertheless, detoxification alone, achieved by means of hemosorption, is also insufficient for the full therapeutic effect, since the body remains in a state of immune suppression, due to which there has been created possibility of developing this severe complication. More stable result is achieved by performing **plasmapheresis** with replacement of removed plasma from the patient with "incompetent" antibodies, immunoglobulins, complement, opsonins to native plasma, above immune components of which immediately begin to fight against pathogens and other pathological products. This provides more reliable results, particularly when replacing the plasma in volume close to patient’s CPV. In this case, to be fair, it is necessary to emphasize that this is actually not so much of plasmapheresis as **plasma exchange**. After all, in terms of hypoproteinemia it is impossible to remove even a small volume of plasma without its immediate replacement for the donor one at a ratio of 1:1. In recent years we have almost completely switched to this tactic [Voinov V.A. et al, 2007, 2013].

Now we present the analysis of treatment 153 patients with varying degrees of RDS. All they received traditional medical therapy, and at the development of respiratory failure – artificial lung ventilation (ALV) with a positive end-expiratory pressure (PEEP).
Allocated 3 degrees RDS – moderate, severe and highly severe, focusing on the level of hypoxemia, medium weight oligopeptides ("middle molecules") and to the area and intensity of lung shading at X-ray examination (Table 2).

### Initial clinical laboratory factors with different degrees of severity of RDS

<table>
<thead>
<tr>
<th>RDS degree</th>
<th>Severity criteria</th>
<th>Middle molecules level</th>
<th>PaO₂</th>
<th>Area of lung shading in X-Ray</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Moderate</td>
<td>50.0±22.5</td>
<td>68.2±1.8 (at FiO₂ 0.4)</td>
<td>Lower sections (or sources)</td>
<td>Self-maintained</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
<td>444.2±45.3</td>
<td>60.3±0.8 (at FiO₂ 0.7)</td>
<td>Lower and middle regions</td>
<td>ALV+PEEP</td>
</tr>
<tr>
<td>III</td>
<td>Highly severe</td>
<td>680.1±52.6</td>
<td>44.7±0.9 (at FiO₂ 1.0)</td>
<td>Complete hepatization of lungs</td>
<td>ALV with PEEP</td>
</tr>
</tbody>
</table>

Allocation of patients according to the degree of evidence of RDS is presented in table 3.

### Allocation of patients according to the degree of evidence of RDS and methods of treatment

<table>
<thead>
<tr>
<th>Degree RDS</th>
<th>Methods of treatment</th>
<th>Control</th>
<th>Detoxification</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Moderate</td>
<td>52</td>
<td>47</td>
<td>99</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
<td>15</td>
<td>29</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>Highly severe</td>
<td></td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>67</td>
<td>86</td>
<td>153</td>
</tr>
</tbody>
</table>

Among patients with moderate RDS there were no deaths, but the duration of the treatment using the methods of detoxification was significantly shorter – 28.0±1.5 versus 40.3±3.3 days in the control group (p<0.05). The mortality rate for severe and highly severe degree of RDS is presented in Table. 4. It should be noted that a
subgroup of patients with a highly severe RDS treated with only traditional methods did not stand alone, because in such cases the mortality rate was 100%.

Table 4.

Mortality rate for different degrees of RDS depending on the methods of treatment

<table>
<thead>
<tr>
<th>Degree of RDS</th>
<th>Methods of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only traditional</td>
</tr>
<tr>
<td>I</td>
<td>Moderate</td>
</tr>
<tr>
<td>II</td>
<td>Severe</td>
</tr>
<tr>
<td>III</td>
<td>Highly severe</td>
</tr>
</tbody>
</table>

As seen from the table, even with moderately-severe RDS use of detoxification allows faster and more reliable arresting of acute lung injury, but in severe cases it is reflected also in the overall outcome of the disease. It should be noted that the earlier methods of detoxification were used, the more expressed and evident was their effectiveness. Thus, as a rule, it was enough to have just one session hemosorption or plasmapheresis with UV or laser irradiation and indirect electrochemical oxidation of blood to provoke a turning point in the course of the disease and subsequently the body itself, and at a lower level of medical support, would cope with new complications. Severe cases of RDS often require repetition of two or three sessions of detoxification to achieve stabilization and regression of lesions of lungs, but their belated application is not able to save all the patients.

With extremely severe cases of RDS with almost total lung damage develop severe pulmonary parenchymal respiratory failure, not corrected by any means of mechanical ventilation. In these cases, ECMO provided a more rapid normalization of gas exchange, and carried out in parallel intensive detoxification (up to three sessions per day) contributed to the elimination of toxic edema of the lung parenchyma with restoring the degree of "airiness" at lung X-ray examination after 7-15 hours, and by the end of ECMO they managed to recover quite a satisfactory level of gas exchange function of the lungs.

Overseas ECMO became far more widespread and its performance in recent years has increased to 47-60% [Bartlett R.H. et al., 1996; Kolla S. et al., 1997], but to
achieve stable restoration of gas exchange it usually takes from several days to two weeks of such treatments. And at the same time none of detoxification methods are generally used. In our practice, with parallel hemosorption it is sufficient to have 20-44 hours of ECMO [Voinov V.A. et al., 1995].

But more stable result is achieved through conduct of plasmapheresis with replacement of remote plasma of the patient with "incompetent" antibodies, immunoglobulins, complement, by native plasma, above mentioned immune the components of which immediately begin to fight against pathogens and other abnormal products.

It should be noted that this approach not only normalizes the humoral but also cell-mediated immunity since a complement does not occur without opsonization receptors of macrophages, without which it is not possible to capture and subsequently destroy pathogens. This provides more reliable results, particularly when replacing plasma volume approaching CPV of the patient and this is actually not so much of plasmapheresis as a plasma exchange. Indeed, in a hypoproteinemia we cannot remove even a small volume of plasma without immediately replacing it with a donor at a ratio of 1: 1. Recovery of the level of immune protection is also facilitated by photohemotherapy and indirect electrochemical oxidation potentiates detoxification. And in recent years, we have almost completely switched to such tactics.

An example of such a leading role of endotoxemia and immunosuppression on the emergence and development of life-threatening RDS and effectiveness of detoxification is the following clinical observation.

Total lung damage with severe multiple organ failure developed in a patient S., 40 years old, suffering from sarcoidosis, long-term history of use of steroids. Gradually deepening immunosuppression determined the scale and speed of progression of respiratory infection. By the beginning of efferent therapy the patient was in a critical condition. ALV with PEEP did not correct parenchymal hypoxic respiratory failure and coma. X-ray examination revealed an intense and almost total shading ("hepatization") of the lungs. Hepato-renal failure manifested by significant fluid retention in the body with an increase in serum creatinine, bilirubin and transaminases. Central hemodynamics was maintained by sympathomimetics, frequent group politopnye ventricular extrasystoles were detected.

Donor plasma was not available, so the first phase of efferent therapy aimed at detoxification included hemosorption 6 liters of blood with its laser irradiation and indirect electrochemical oxidation. The next day the condition stabilized to some degree. 500 ml of urine was received. X-ray showed signs of airiness in upper part of lungs.
Almost recovered was the normal rhythm with single extrasystoles, sympathomimetics were cancelled.

At that, the repeated screening of efferent therapy was conducted - membrane plasmapheresis with exchange of 1500 ml of donor fresh frozen plasma to and with laser irradiation and indirect electrochemical oxidation of the blood. The next day, we observed recovery of consciousness and spontaneous breathing, followed by a more rapid recovery of lung function and other vital organs and complete recovery.

Massive plasma exchange leads to a more rapid normalization of homeostasis. Unlike hemosorption, there is not only a more reliable and complete removal of all pathological products, regardless of their electrochemical activity, but also a full recovery of all plasma components – proteins with normalization of oncotic pressure and volemic balance, hormone-enzyme activity with recovery mechanisms of autoregulation [Nedashkovsky E.V. et al., 1999]. All this allows to completely prevent the dramatic scenario of RDS development and provides a more rapid and full improving, meaning the regression of a toxic edema of the lungs and other organ failures, a complete restoration of their functions and ultimately – recovery [Voinov V.A., 1995, 2013; Gromov M.I., 1996]. Use of plasmapheresis with photomodification of blood in cases of patients with acute pneumonia reduced the time of their stay in a hospital bed from 24.1 to 19.9 days, increased frequency of full recovery from 21.6 to 42.9% and prevented deaths [Karmanova I.V., Lujnova T.M., 2002].

The same positive effect was achieved with the use of detoxification (membrane plasmapheresis), in cases of respiratory distress syndrome or neonatal RDS, including seriously premature children with weight of up to 700g in which cases the surfactant deficiency is the main pathogenetic mechanism of lung lesions. At the same time without any additional surfactant for several hours on X-ray examination we could also see recovery of lung airiness [Voinov V.A., 2005].

Thus, no fully satisfactory results of using a surfactant on one hand, and the achievement of much better results in the application of methods of detoxification in cases of RDS, on the other hand, suggests that the true reason for the drop of surfactant activity is its inhibition by toxic substances penetrating into the alveolus with toxic violation of vascular permeability. This introduced exogenous surfactant, as well as the natural one, is affected by these toxic substances and stops its activity.

Use of detoxification, promoting the elimination of porosity of vessels is a more pathogenically reasonable treatment in cases of RDS, as after the termination of admission to the alveoli of toxic substances in the coming hours there is a restoration of
reproduction of natural surfactant, which makes it unnecessary the need for the exogenous drugs.

In the treatment of RDS and multi-organ failure is also used hemofiltration using highly modern hemofilters allowing to remove all components of blood plasma with a molecular mass of less than albumin. With an adequate replacement for the day can thus be removed more than 20 liters of liquid. Nevertheless, not all pathological products can be removed by hemofiltration. In particular, at high removal of cytokines such as TNF-α and IL-1β, other cytokines – IL-6 and IL-8, more adverse prognostic, detained in the body. With hemodiafiltration we can reduce and IL-4 with correction flow of critical states, levels of TNF-α, IFN-γ and corrected course of critical states, however, such a procedure is not always influences the course of infection. Last was corrected only using plasmapheresis, contributed to the recovery of decreased production of IFN-γ and improvement of cellular and humoral immunity. Used also the combination of plasmapheresis with constant hemofiltration [Schmidt J. et al., 2000].

For a more complete recovery of immune mechanisms is also advisable to mix as hemosorption and exchange plasmapheresis with methods of quantum photo-hemotherapy.

Example described above in more detail, revealing the pathogenesis of RDS and the rationale for the use of methods of efferent therapy in the development of this complication, and reflects a number of other clinical situations arising from severe burns and trauma, acute inflammatory diseases of the abdominal cavity, etc. In all these cases, the efferent therapy, however, can not provide stable effect without elimination of toxicity source, typically by surgical methods. But sometimes without prior detoxification is impossible to ensure the safety conditions of surgery and after surgery efferent therapy promotes more rapid normalization of homeostasis, more complete and sustained recovery.

Let us examine some of the features of different approaches to clinical situations.

**Acute renal failure**

As noted above, adult respiratory distress syndrome is never isolated. It is often accompanied by a lesion in one degree or another, and other vital organs also, primarily kidney. Acute renal failure (ARF) occurs in one third of patients with acute pneumonia {Murugan R. et al., 2009}. It has long been observed that even on its own ventilation, especially with a positive end-expiratory pressure (PEEP), reduces renal blood flow by
32%, glomerular filtration rate by 19% and urine output by 34% [Annat G. et al., 1983; Ko G.J. et al., 2009; Koyner J.L., Murray P.T., 2010].

Acute kidney injury (AKI) often develops with sepsis or sepsis joins with already developed kidney disease [Schrier R.W., Wang W., 2004; Bouglé A., Duranteau J., 2011; Mehta R.L. et al., 2011]. Risk factors include severe burns, pancreatitis and peritonitis, traumatic shock syndrome and prolonged compression, eclampsia [Mosier M.J. et al., 2010; Serov V.N. et al., 2011]. Mortality in this case reaches 70-80% [Ko G.L. et al., 2009; Chou Y.H. et al., 2011].

Nevertheless, as with RDS, a variety of etiological factors in the pathogenesis of AKI is toxic damage of the renal parenchyma. Violations of the permeability of vascular endothelium lead to perivascular edema with decreased renal blood flow, glomerular filtration, tubular necrosis, oligo-anuria [Bouglé A., Duranteau J., 2011]. According to the consensus reached at the conference working group on ARF (ADQI), the criteria for inclusion of patients at “risk” group is decreased urine output less than 0.5 ml/kg for 6 hours; to a group of "kidney damage" – less than 0.5 ml/kg 12 hours; the group "renal failure" – less than 0.3 mL/kg within 24 hours or “anuria” for 12 hours [Bellomo R. et al., 2004]. The risk of death in the group of "risk" – 13%, in the "damage" – 40%, and "failure" – 80% [Steinvall I. et al., 2008]. But the survivors in the long term often showed signs of chronic renal failure [Lo L.J. et al., 2009; Hsu C.Y. et al., 2009]. At the same time, despite the efforts methods of renal replacement therapy (continuous or intermittent hemofiltration) after discharge from hospitals the mortality during in the first year was 23%, and for the second year still 7.6%, which ultimately was 65.7% [Van Berendoncks A.M. et al., 2010].

Such unfavorable prognosis in ARF, of course, require intensive care. However, as with RDS, respiratory failure when trying to heal through various methods of mechanical ventilation, acute renal failure and renal excretory function disorders tend corrected through measures to remove the accumulating fluid by different methods of hemodialysis or hemofiltration [Lins R.L. et al., 2009; Lo L.J. et al., 2009; Abe M. et al., 2010; Chawla L.S., 2011].

And in both cases, this approach is explained by the desire to eliminate the only visible disorder – breathing with RDS and diuresis in ARF. That is, it was actually symptomatic therapy which does not affect the essence of the pathology – endotoxemia underlying these organ disorders. And really – mortality in these patients remained quite high – up to 50-70%, regardless of the choice of methods "renal replacement therapy " – dialysis, hemodiafiltration, intermittent or continuous veno-venous hemofiltration
[House A.A., Ronco C., 2008; Russel J.A., 2008; The VA / NIH Acute Renal Failure Trial Network, 2008; Palevsky P.M. et al., 2009; Zakharov M.V., 2010]. Even after normalization of water balance lethal lesions often occurs due to other organs in the first place – lungs [Paladino J.D. et al., 2008]. Using only hemofiltration impossible to remove macromolecular least toxic products, including fibrinogen, which makes even against the background of hemofiltration, still have recourse to plasmapheresis [Fülöp T. et al., 2011]. This confirms our belief that purely symptomatic therapy (removal of excess fluid) does not eliminate the problem of endotoxemia – the main factor of tanatogenesis.

It seems more reasonable an active detoxification – hemosorption or plasmapheresis. And indeed, almost always after removing "toxic press" from the kidneys occurred restoration of their excretory function. The very next day diuresis was not less than 500-700 ml, which can be seen in the above clinical observation. In parallel, improved functional status also other vital organs – lungs, liver, heart, brain [Voinov V.A. et al., 1995].

Especially revealing was the treatment of woman with a complete anuria on the background of eclampsia, which lasted for a month after delivery. After the session hemosorption on the next day diuresis was already 500 ml, and after repeated sessions it recovered fully followed by a rapid recovery of the patient.

**Acute cholecystitis**

Intoxication syndrome in acute cholecystitis is a combination of inflammatory mediators, bilirubin and trasferases and the growing pool of BAS stimulated decrease in liver detoxification function. The surgical treatment of the use of efferent therapy may be indicated preoperatively also – to reduce the high levels of bilirubin and other components of endotoxemia and better prepare for surgery. This is especially true in cases of unsuccessful attempts to decompress biliary tract or ineffective biliation after surgical decompression. Optimal is performing of plasma exchange with removal of 1500-2000 ml of plasma and replacing it with an adequate amount of donor fresh frozen plasma the day before draining operation. A clear connection between the level of accumulation of acute phase proteins ($\alpha_1$-antitrypsin, interleukin-6, C-reactive protein), accompanied by hypoalbuminemia, with the risk of postoperative complications, including death [Haupt W. et al., 1997].
After surgery, optimally 2-3 days after it, efferent therapy is to prevent acute liver failure, and in the subsequent period for its treatment. And here in the foreground also goes plasmapheresis. In the presence of severe intoxication with hypoproteinemia plasma removal of the patient must be replenished mainly donor plasma.

**Pancreatitis**

This disease is the presence of severe endotoxemia on the basis of sharp increase of proteolytic enzymes and the resulting increase in the content of the middle weight molecular substances, activation of lipid peroxidation with the suppression of the antioxidant defense system. In this first liver takes the brunt of the enzymes in the blood washed out of the pancreas, to a certain point, retaining the ability to inactivate them, and then comes lesion its functions of detoxification, which defines the transition to the decompensated phase of endotoxemia with the growing level of transferases, phenol, ammonia, fatty acids and other toxic metabolites [Saveljev V.S. et al., 1999]. Increased their content, particularly free fatty acids, promotes lung parenchyma lesions and the development of respiratory distress syndrome [Elder A.S. et al., 2012], which was confirmed by the results of experiments on animals also [Rosen H.R., Tüchler H., 1992].

On the other hand, with operations on the biliary tract with prolonged jaundice and endotoxemia surgery itself contributes to further release of many biologically active substances. In addition, exacerbation of cholangitis and liver failure in the early postoperative period worsens endotoxemia and often contributes to the development or exacerbation of pancreatitis, which can negate all the results of the operation.

One of the characteristic manifestations of pancreatic necrosis is systemic inflammatory response and sepsis. Septic shock is characterized by persistent hypotension not corrected by adequate completion of CBV, and multiorgan failure accompanied by damage to the functions of vital organs when homeostasis can not be restored without intensive therapeutic interventions.

All this justifies the need for the inclusion of efferent therapy at the **earliest stages** of the disease, as endotoxemia, as well as in the case of RDS with pneumonia, exacerbated disturbance of functional state of the pancreas, helps to increase output enzymes, thus closing the vicious circle. Application of plasmapheresis in 1-3rd day of onset allows almost refuse to perform early laparotomy in severe acute pancreatitis and significantly reduce the frequency of their performance when it extremely difficult course. Plasmapheresis can significantly reduce mortality in hemorrhagic forms from
70% to 30%, with necrotic – from 49% to 25%, and in all forms of abortive course necrotizing pancreatitis – from 29% to 7% [Krasnorogov V.B. et al., 1998; Gendel L.L. et al., 2003].

Plasma exchange is also useful in preparation for surgery, and the next day after surgery, and after each extended cleaning of surgical wound or relaparotomy. Even more effective was plasmapheresis with simultaneous plasmasorption. Moreover, in such cases, methods photohem- and oxidative therapy (laser irradiation and ozonation of blood) significantly potentiated the effects of detoxification and efferent therapy. Proposed methods and high-volume plasmapheresis with removal of 100% CPV with replacement crystalloid solutions (1.5 CPV) and 10% sodium hydroxethylstarch (Pentastarch Infukol) to 0.5 CPV [Dubchenko S.G., 2000].

At the same time, plasmapheresis stand such patients is much easier than hemofiltration. In addition, if after plasmapheresis content of dead leukocytes in venous blood was reduced by an average of 39.1%, the prolonged veno-venous hemofiltration had no significant effect on their content. In some cases it is advisable to mix plasmapheresis with hemosorption.

Acute pancreatitis often occurs when hyperlipidemia (hypertriglyceridemia), and in such cases plasmapheresis also has a significant therapeutic effect [Routy J.P. et al., 2001; Coman T. et al., 2003; Iskandar S.B., Olive K.E., 2004; Kariakidis A.V. et al., 2005; Al-Humoud H. et al., 2008; Kfoury-Baz E.M. et al., 2009; Martin D. et al., 2009; Stefanutti C. et al., 2011; Syed H. et al., 2010; Ewald N., Kloer H.-U., 2012]. The most significant decrease in the blood levels of triglycerides (from 83.48 to 4.09 mmol/L) was achieved by using cascade plasmapheresis [Zhang G. et al., 2008]. Acute pancreatitis can be caused by systemic lupus erythematosus and thrombotic microangiopathy, and here plasmapheresis also finds its application [Tominaga N. et al., 2008; Chang H.H. et al., 2010].

**Peritonitis**

Peritonitis accompanied by severe endotoxemia due to several confounding factors. As a result, as the active antibiotic, and mobilizing the internal defenses of cellular and humoral immunity, take place a massive lysis of bacteria and destruction of blood cells themselves in the process of phagocytosis with release of an enormous amount of endo- and exotoxins. The latter, together with the products of alteration of tissues and inflammatory mediators are material substrate of the first wave of
endotoxemia during the first days of the disease. Endotoxins contribute to the release and other biologically active substances – histamine, serotonin, prostaglandins, products of the kallikrein-kinin cascade. System is activated and lipid peroxidation with inhibition of antioxidant potential and oxidative phosphorylation. There are conditions for the development of DIC and uncontrollable coagulopathy [Eryuhin I.A., Shashkoff B.V., 1995].

In addition to the presence of endotoxins in *Escherichia coli* and other gram-negative organisms, high suction capacity and a large area of the peritoneum, there is an additional source of income in the blood of endotoxins from the intestinal lumen as a result of activation of putrid fermentation when paresis when sharply increases the permeability of the intestinal wall to such toxins as indole, phenol, scatole, putrescine, cadaverine.

The massive accumulation in blood of a variety of endotoxins in conditions of exhaustion and failure natural detoxification systems leads to persistent toxemia, determining the toxic stage of peritonitis. The main consequence of toxemia is a violation of the permeability of cell membranes, mainly of vascular endothelium, with the development generalized toxic edema of the interstitium with dysfunction of vital organs. The main burden of detoxification has the liver, but it herself, as in pancreatitis, almost first exposed to the toxic shock, because the system of portal vein drains almost all sections of the intestine and peritoneum. As a result, toxic degeneration of the liver tissue itself begins to secrete a toxic substance at least, closing the first vicious circle of endotoxemia. At the same time, creates a special danger ammonia, leading to osmotic disorders and brain edema [Vaquer J., Butterworth R.F., 2007]. Second round occurs after toxic damage the renal parenchyma, and the violation of their excretory function (less than 30 ml/h) leads to greater accumulation of endotoxins.

All of these factors continue their negative impact even after the elimination of the source of peritonitis, being a major factor tanatogenesis. This is confirmed by observations in a happy picture of the state of the abdominal cavity after surgery, but, unfortunately, already ... at autopsy.

Moreover, the surgery itself is an additional load on the system of protection and deepening endotoxemia often develops immediately after the operations. Mortality in peritonitis can reach 38%, with the development of septic shock with hypotension requiring inotropic support, mortality increases to 62%, and in extreme cases, when assessing the scale of APACHE II score more than 30, mortality rate reaches 82% [Gelfand E.B. et al, 2000].
All this makes the sound conducting complex intensive courses detoxification, efferent-, photohemo- and oxidative therapy. In this massive plasma exchange with donor fresh frozen plasma replacement of removed plasma in the amount of 0.7-1.2 CPV promotes more rapid recovery and quality as biochemical homeostasis and activity of immune protection [Vaguero J., Butterworth RF, 2007].

**Traumatic illness**

This term is more capacious, and includes not only certain kinds of damage various organs and tissues, but also consistently developing endogenous intoxication syndrome due to primary "stress-induced storm" of various biologically active substances arising from the traumatic shock and absorption into the blood products of tissue disintegration and subsequent inflammation, especially in the presence of local ischemic disorders ("crush syndrome", syndrome "harness" and long compression, reperfusion syndrome). In a direct and mechanical damage due to prolonged ischemia muscles release myoglobin into the circulation, which is the main cause of acute renal failure after major trauma. Feature is the presence of posttraumatic endotoxemia light gap between the trauma and shock, followed by the onset of symptoms of toxic disorders.

Conducting plasma exchange as early as 6 hours after admission to the hospital to reduce the incidence of acute renal failure in this group of patients by 18%. In such cases, replacement of 1.5-6.0 liters of plasma resulted in a significant reduction in serum myoglobin [Gendel L.L. et al., 2003]. Patients with reperfusion syndrome plasma exchange sessions allow reverse manifestations of renal failure and save limbs. This applies to the operations of large fragments of limb replantation. Plasma exchange immediately after surgery prevents the development of multiple organ failure in the early postoperative period.

Methodology of single-needle manual membrane plasmapheresis with Russian plasmofilter "Rosa" allows to bring the performance of such procedure directly to the scene from experience airmobile hospital of Russian Ministry of Emergency Situations [Popov A.S. et al., 2007]. At the same time, we must remember that in case of natural or man-made disasters at 25% of victims are injured with the development of long-term compression syndrome, in which the mortality rate reaches 30-70%. In such cases, the
membrane plasmapheresis should be held no later than 2 hours after removal of the victims. This provided a positive clinical effect in all affected [Popov A.S., 2011].

On the second or third day after the elimination of all primary trauma manifestations begin RDS and other disorders of the vital organs. This does not mean that it was the true light interval. Endotoxemia not only weakened, but even grew, but impairment of function of the affected organs began to appear only after significant abuses. We have already mentioned that the clinical manifestations of RDS occur only after a two-fold excess extravascular fluid volume of the lung. Same thresholds exist and to manifestations of other organ failure.

At the same time, this light interval is optimal for the treatment and prevention of detoxification and efferent therapy – when it reduced the risk of renewed bleeding, but not yet due irreversible disorder of hemodynamics, gas exchange, excretory functions and detoxification with organic lesions of the parenchyma of the relevant organs. But even with already ensuing multiple organ failure and septic complications of the use of plasmapheresis and hemoperfusion through endotoxin adsorbent allows faster to patients in serious condition [Wei Q. et al., 2009].

Minimum allowable period for heparinized blood needed for hemosorption after trauma, surgery, and hemostasis is 6 hours. But hemosorption as well as plasmapheresis can also be carried out without heparinization, so they can start in the first hours after the initial stabilization, even when uncertainty in complete stop internal bleeding. It is of the utmost importance in the syndrome of prolonged compression (“crush-syndrome”) – timely removal from the circulation of products of autolysis and tissue hypoxia, myoglobin (after crush large muscle mass) and free hemoglobin (at hemolysis) prevent the development of severe renal insufficiency, and obviate the need to follow-up (and often is unsuccessful) sessions hemodialysis. In particular, the use of hemodialysis did not prevent the development of acute renal failure, the need for amputations and even deaths [Li W. et al., 2009]. Belated start detoxification and efferent therapy occurring against a background of severe organic disorders will not give the possibility to achieve a decisive breakthrough in the treatment of multiple organ failure.

Note that after severe injuries develop immunosuppression by reducing the number of mature T-lymphocytes (CD3⁺), T-helper cells (CD4⁺) and cytotoxic cells (CD8⁺), which against the backdrop of increasing levels of cytokines (IL-1β and TNF-α) requires not only detoxification but immunocorrective plasma exchange. Timely use of plasmapheresis in these patients reduces the duration of treatment, the number of used
antibiotics and other medicines to reduce the risk of deaths. There are reduction of the
dicators of toxicity (leukocyte index of intoxication) in 3-4 times, and systemic
inflammatory response (2-3 fold leukocytosis, acute phase proteins of 30%), creatinine
(45%) and bilirubin (40%), improves the coagulation system.

E.V.Gembitsky et al. (1996), on the experience of the war in Afghanistan, was also
considered a leading of endotoxemia in cause RDS virtually all wounded with severe
head injuries and associated lesions of other areas of the body and limbs, so in the
program have found it appropriate therapeutic measures including plasmapheresis, as
the most effective method of detoxification. These concepts have been confirmed in the
"peaceful" time also. Plasmapheresis allowed more quickly reduce the concentration of
middle weight molecules (MWM), indicators leukocyte index of intoxication and reduce
the incidence of extracranial complications (ARF, pneumonia, sepsis) [Kustov I.A. et al.,
2001].

Indications for efferent therapy occur after heavy and prolonged operations, in
particular, open heart surgery with cardiopulmonary bypass. In this, we ourselves have
seen in the study of the causes of postperfusion pulmonary syndrome when they found
a progressive increase in toxic middle weight oligopeptides from the start of the
operation and reaches a maximum value for its end. Introduction sorption column in the
extracorporeal circuit perfusion prevented the growth of not only the content of MWM,
but also reduce the severity of lung injuries and other vital organs and improve the
outcomes of such operations. The same results are obtained also by conducting the
early therapeutic plasmapheresis in the first 2-6 hours after these operations.

All adverse perioperative factors cause ejection of a plurality of pathological
agents: cytokines, free radicals and so on, which have a damaging effect on the various
organs and systems, development coagulopathy including disseminated intravascular
coagulation (DIC), infections and complications of multiorgan failure. In this case, the
entire spectrum of methods of extracorporeal detoxification only plasma exchange
allows the most efficient to remove them and to provide a more favorable postoperative
period and the overall outcome of such operations.

This applies to a number of other traumatic operations performed without
cardiopulmonary bypass. In particular, plasmapheresis on the first day after aortic
surgery helps reduce blood viscosity, fibrinogen and D-dimers and improve treatment
outcomes.

Rhabdomyolysis with mioglobulinemiya may arise not only from massive injuries.
This occurs after intense workouts, and under the influence of various drugs (statins)
and toxins, infections (bacterial shock, tularemia, salmonellosis). In such cases it is also advisable efferent therapy.

**Burn disease**

In extensive burns can also be noted in two waves during endotoxemia. Immediately after the injury occurs intense absorption products acute tissue destruction zones of thermal injuries, increases the content of free hemoglobin due to the destruction of red blood cells in the blood vessels adjacent to these areas. Lysis and resorption of the decay products of necrotic tissue causes a cascade of endotoxin reactions with release of cytokines, TNF-α, platelet activating factor, leukotrienes, lipid peroxidation products with the development of systemic inflammatory response syndrome, which determines the severity of the burn injury.

As a result of severe endotoxemia occurs intensive due to loss of protein into the body because of the toxic porosity vascular endothelial and interstitial edema, as well as outside getting wet with abundant burn the surface of the skin. It is also accompanied by blood clots and additional disorders of blood rheology and microcirculation. It takes place also progressive depletion and inhibition of both cellular and humoral immunity. During this period, one of the main "target organs" for various endotoxins is lung, which develops toxic destruction of the vascular endothelium, leading to RDS. Disorders occur in intestinal epithelium with translocation also of *E. coli* and intestinal enterotoxin on 1-3 days after severe burns [Al-Ghoul W.M. et al., 2004]. Often develops acute kidney failure with a transition to multi-organ failure [Mosier M.L. et al., 2010].

In this phase of the primary endotoxemia require detoxification and efferent therapy – only removal of toxic plasma with replacement of native donor plasma can give the maximum therapeutic effect. At the same time, plasmapheresis may be performed in a stage of burn shock [Nazarov I.P. et al., 2002; Klein M.B. et al., 2009; Endorf F.W., Dries D.J., 2011]. Positive results were achieved in haemofiltration with a volume of fluid removal to 6-12 liters. However, after plasmapheresis and removal "toxical press" from kidney, diuresis increased by 400% [Neff L.P. et al., 2010], which makes it sound more than just the removal of excess water from the body. Much more important is to restore its own renal excretory function. Attempts to carry out simple infusions of plasma and protein drugs without liquidation of the causes of endothelial porosity appear to be ungrounded.
Breach of the skin barrier function with large gate for infection, on the one hand, and depression of immunity occurs due to severe primary endotoxemia, on the other, create the conditions for inflammation, suppuration lesions and sepsis with the increase of the second wave of endotoxemia. Hemosorption allows in such cases, reduce the appearance of endotoxemia. However, a more complete removal of toxic metabolites and also incompetent immune system components and replacing them with full-fledged at plasma exchange able to solve the problem of detoxification and as well as immune stimulation.

**Freezing cold injury**

Significant scale tissue destruction with frostbite also accompanied endotoxicosis, especially in the development of necrosis of the distal portions of the limbs and cutting off their long overdue. Furthermore, while uncommon homeostasis disorder at concomitant prolonged general hypothermia. It also raises the question of intensive detoxification and efferent therapy to prevent the development of multiple organ failure.

**Sepsis**

Despite all the advances in the treatment of infections and critical states, purulent-septic complications in surgery is one of the common causes of deaths [Nalesso F., 2005]. In particular, the frequency of postoperative sepsis U.S. reaches 4.24%, and severe sepsis is thus observed in 2.28% of patients [Vogel T.R. et al., 2009]. In this case, the summary statistics indicate a significant frequency of sepsis, reaching 751,000 per year, of which 383,000 patients requiring intensive care, and 130.000 – mechanical ventilation. The frequency of these complications increases by 1.5% per year. Mortality rate is 28.6%, and the cost per patient – $ 22.100. The general costs of caring for these patients in the United States account for 16.7 billion dollars [Angus DC et al., 2001]. In pediatric patients with sepsis number reaches 42,364 with case fatality rate of 10.3%. Treatment costs of one such child reach $ 40.600, and the total cost to 1.96 billion dollars a year [Watson R.S. et al., 2003]. In Western Europe, the cost of treating one patient with sepsis constitute 23.000-29.000 Euro [Burchard H., Schneider
Sepsis, obviously, is more common than its documented in the laboratory detection of various microorganisms in blood cultures. This is largely due to the early onset of antibiotic therapy in the event of inflammatory diseases and complications. The above results playback acute pneumonia in animal experiments have shown that even 15 minutes after intratracheal administration in healthy animals culture pathogenic pneumococci their ever found blood cultures or smears of slices of liver, kidney and spleen Therefore, almost any particularly severe, inflammatory complications can assume the presence of pathogens not only in wounds or damaged organs, but also in circulation.

It should be noted that the very development of an acute infectious process could be due to the initial immunodeficiency that developed as a result of recently transferred other diseases (even the common respiratory viral infections), adverse environmental or social factors of chronic intoxication (alcohol, drugs, etc.), not to mention the classical HIV. Proof of this is often observed lymphopenia and leukopenia at the initial stage of the disease.

Further developing the chain of events worsens. Immune system mobilizes all its reserves to combat infectious and other agents that are not unlimited, and eventually it comes exhaustion. Increase endotoxemia acts overwhelmingly all components of cellular and humoral immunity leading to an even more profound immunosuppression, which may be described as "immune distress syndrome."

Described the development of endotoxemia in critical conditions often described as "systemic inflammatory response syndrome" (SIRS), which may be the answer not only to infection and sepsis, but also to any aggression and traumatic stress. Thus the foremost proinflammatory mediators, primarily cytokines, such as IL-1 and TNF-α, as well as degradation products of neutrophils, platelets and coagulation factors, complement fragments, derivatives of arachidonic acid, "granulocyte-colony stimulating factor" [Bone R.C., 1996; Stegmayr B., 1999; Weiss M. et al., 1999]. Yet it is not clear what causes circulating cells (macrophages, neutrophils, platelets) sent to places of injury or infection and how they interact with the vascular endothelium. It is not clear and escalating this, in general, positive biological response in a state of shock and subsequent multiple organ failure and death. We should note also the role of the accumulation of free fatty acids in organ lesions, particularly in the groups of patients who died (6.88±0.13 mg/ml) compared to survivors (3.85±0.48 mg/ml) [Nogueira A.C. et al., 2008].
Such excessive reactions are often counterproductive and themselves contribute to the development of septic shock, multiple organ failure and RDS. In the blood plasma increases rapidly content acute phase proteins synthesized mainly in the liver. They affect hemostasis (fibrinogen), phagocytosis and bactericidal (complement, C-reactive protein). They may be antithrombogenic \((\alpha-1\text{-acid glycoprotein)}\), antiproteazny \((\alpha-1\text{-antitrypsin, } \alpha-1\text{-chymotrypsin)}\), antioxidants (ceruloplasmin, glutathione). The concentration of C-reactive protein, normally extremely low, with such systemic inflammatory response rapidly increases by 10-100 times, which often reflects the scale of the manifestations of this pathology [Bistrian B.R., 1999]. More than 50% of cases in the genesis of septic complications plays a significant role Gram-negative bacteria, and the leading role are lipopolysaccharides that are permanent structural components of the cell membrane of these bacteria. With considerable frequency of septic shock in the U.S. - up to 500,000 patients per year, of which 100,000 die, this problem is extremely urgent [Palombo J.D., Bistrian B.R., 1999].

However, the body in response to such aggression forms and anti-inflammatory response, as a compensatory (systemic anti-inflammatory response syndrome - SARS). This generates another class of biologically active substances: these are interleukins 4, 10, 11 and 13, the growth factor-\(\beta\), colony-stimulating factor, circulating receptor-antagonists TNF-\(\alpha\) and IL-1. These mediators are still poorly understood, however, proven by their inhibition of monocytes, T- and B-lymphocytes, including proliferation of antigen-specific T-lymphocytes. As a result, developing immunosuppression, which sometimes can be very deep. This is especially dangerous, given previous immunosuppression, as well as increases one with the severity of patients with septic complications. Moreover, these mediators may even suppress their own synthesis, thereby providing a restoration of homeostasis. These reactions are characterized as "compensatory anti-inflammatory response" [Bone R.C., 1996]. The interaction between these pro-inflammatory and anti-inflammatory mediators is presented as a battle of opposing forces. If there is a balance of these forces, the homeostasis is restored. If not – then develops one or the other reaction. At the same time, and in both cases it is possible dramatic developments death.

Thus, septic complications develop as severe endotoxemia on the background of increasing immunosuppression, resulting in a vicious cycle to break that neither the body nor the most intensive medical therapy is not able to.

Detoxification using hemosorption can stabilize the patient's condition [Stegmayr B.G., 1996, 2000; Rimmele T., Kellum J.A., 2011]. While on the sorbent may be delayed
both living and dead microorganisms already. Derived from circulating also leukocytes overloaded with microbes that prevents their adhesion to vascular endothelium, particularly in the areas of its lesion of circulating toxic products, with subsequent theirs decay and further destruction of endothelial ("WBC regional standing" syndrome). Furthermore, the sorbent also retained the most adhesively active platelets that, when returning into the bloodstream, may be as nuclei for formation of platelet aggregates with the excitation of successive stages of DIC.

We were convinced of our own experience, spending in the 80s hemosorption for patients at the height of "Pseudomonas" sepsis. In the culture of blood flowing into the sorbent, and the sorbent itself after the procedure, identified the abundant growth of this pathogen, while the blood flowing from the sorbent caused growth only single colonies. Thus for the total elimination of sepsis sometimes there were required to hemosorption 5-7 sessions.

Nevertheless, even after the most active sorption detoxification body is unprotected against microbes. Perhaps the development and secondary fungal or viral organisms, against which antibiotics may be powerless and the patient's condition deteriorates again.

Therefore, the most pathogenetic justified the use of plasma exchange when together with removed plasma derived not only toxic products, but also all the incompetent components of the immune system. There are concerns that the loss of immunoglobulin may deepen immunodeficiency. However, these immunoglobulins or antibodies have shown their weakness in the prevention and elimination of the infectious process. In this case all the available active antibodies already are associated with pathological antigens in the form of inactive immune complexes. All available opsonins and complement already been used in previous reactions phagocytosis, making it impossible to capture pathogens even quite normal phagocytes. Fresh frozen donor plasma replacement removed plasma allows you to quickly restore the natural protective mechanisms, without which the most powerful super-wide spectrum antibiotics are powerless, and their hepato- or nephrotoxicity may exacerbate the patient's condition [Ragimov A.A. et al., 2008].

After the massive plasma exchange occurs faster improving of diseases course and reverse the development of organ disorders [Gromov M.M., 1996; Voinov V.A. et al., 1999, 2013; Hjorth V., Stenlund G., 2000; Schmidt J. et al., 2000; Busund R. et al., 2002; Ronco C. et al., 2005]. The authors emphasized that in all cases of septic complications and septic shock as early as possible is necessary to carry out
therapeutic plasmapheresis. Enabling courses of plasma exchange 70%-100% CPV in patients with abdominal sepsis in the early postoperative period (optimally in the first 4 hours after the onset of complications) not only reduced the toxemia, but also effectively stimulated immunity, dropped manifestations of DIC with the restoration of the affected parenchymal organs and 19.5% reduced mortality [Solovyova I.N. et al., 2011].

The courses plasmapheresis proved useful also at septic complications after surgery removal of brain tumors. Using plasmapheresis showed its effectiveness in the treatment of acute purulent mediastinitis [Matveev S.V. et al., 2008; Rey S.I. et al., 2008]. Plasmapheresis managed to remove also associated renal lesions, when in addition to their functions provide replacement and immunomodulatory effects [House A.A., Ronco C., 2008]. Plasma exchange was effective in children with sepsis-induced multiple organ failure [Qu L. et al., 2011]. Even at meningococcal septicemia plasmapheresis in combination with leukapheresis or exchange transfusion of whole blood contributed to the recovery of patients [Bjorvath B. et al., 1984; van Deuren M. et al., 1992].

Over the past 10 years abroad also has increased dramatically the frequency of use of active methods of extracorporeal correction of sepsis, especially in Japan, where the payment for such procedures provided by the State [Kawamura A., 2003]. Besides conventional nonselective plasmapheresis increasingly used the methods of selective adsorption endotoxins and cytokines [Hirasawa H., 2002; Nakae H., 2006]. In particular, it was possible endotoxin removal by selective absorption on the toner fixation on the fibers of polymyxin-B in the case of sepsis and septic shock caused by Gram-negative bacteria. However, the high risk of bleeding due to heparinization is contraindicated for selective sorption of endotoxin [Solovyova I.N., Ragimov A.A., 2011].

However, P. Toft et al. (2008) in experimental animals have shown that non-selective and conventional plasmapheresis sufficiently effective in preventing oxidative stress and the accumulation of granulocytes in the lungs after administration of Escherichia coli endotoxin in a dose of 30 mcg/kg. Especially because if gram-negative flora selective adsorption of endotoxin was quite effective, then the significant increase of mixed flora of survival were observed, and in fact often occurs precisely mixed flora. Furthermore, sorption of endotoxin has no direct effect on the level of intoxication. Even with conventional plasmapheresis negative bacteria endotoxin content is reduced 3.4 times.

Attempts to use different methods of hemodialysis and hemofiltration in the treatment of sepsis showed their low efficiency, since only a small portion of pool
endotoxins was removed [VA / NIH Acute Renal Failure Trial Network, 2008; Mehta R.L. et al., 2011]. When plasmapheresis toxic products removed more fully, there is occur to achieve a more favorable outcome in 80% of these patients [Stegmayr B., 1996, 1999, 2000, 2001; McMaster P., Shann F., 2003; Bellomo R. et al., 2005; Fortenberry J.D., Paden M.L., 2006; Mariano F. et al., 2006]. In addition, in isolated renal replacement therapy there is not adequate recovery occurs immune defense systems [Tetta C. et al., 2003; Ronco C. et al., 2008]. Although Y. Eguchi (2010), using the so-called plasma-diafiltration when passed dialysate around the fibers of plasma-separator, and at the end of the session there is a replacement in 1200 ml of fresh frozen donor plasma, achieved notable success reducing the mortality rate to 36.4% versus the expected 68%. But such success can be explained by the addition of donor plasma, which in fact there was already plasma exchange but with significant complexity and rising costs of such a procedure.

Of course, the presence of acute renal failure associated with decreased rate of diuresis until anuria may justify the use of such filtration methods for removing excess fluid, but it is not the recovery of its own renal excretory function [Yakovleva I.I. et al., 2000]. On the other hand, after hemosorption or plasma exchange, when removed "toxic press" from the kidneys, the next day you can get 500-700 ml of urine with a further positive dynamics.

Positive results were achieved also at the use of plasmapheresis in the complex treatment of obstetric sepsis and septic shock, especially in the early stages of the process, when the mortality rate can be reduced from 80% to 15%, and postpartum women stay in the hospital decreased from 42.4 to 24.6 beds days [Dolgoshapko O.N., 2009].

Plasmapheresis in obstetric sepsis is often performed in partial plasma exchange in two stages. For preoperative preparation after hemodynamic stabilization and elimination of hypovolemia held therapeutic plasmapheresis with removal of 50% CPV with one hundred percent reimbursement of donor fresh frozen plasma. In the early postoperative period after stabilization of hemodynamics, gas exchange and renal excretory function held repeated sessions of plasmapheresis with removal of up to 70% CPV and also with the full replacement of donor fresh frozen plasma [Serov V.N. et al., 2011].

No less difficult septic complications occur in newborns also. Every year they occur in 30 million infants and 1.2 million of them die [Afroso S., 2006].
It must be borne in mind that in septic shock develops extremely critical condition with severe hemodynamic instability. But even in these cases, without detoxification it can not be break the vicious circle of complications, and the very performance of this procedure is high risk. Experience in the use of the Russian device “Hemofeniks” with membrane plasma filter “Rosa”, where the volume of the priming system highways does not exceed 70 ml and a variable volume of about 9 ml of blood, showed the possibility of the success of membrane plasmapheresis, even in cases when the systolic blood pressure is only supported by sympathomimetics at least 90 mm Hg. At the same time could be observed even some stabilization of hemodynamics was allowed to reduce the doses of sympathomimetic, even during the procedure as the elimination of toxic substances.

Naturally, the combined use of laser irradiation of blood contributes to a more lasting effect.

The following clinical observation may serve as an example.

**Girl D., 2.5 years old, weighing 15 kg, suffered from acute lymphoid leukemia.** After high-dose chemotherapy with stem cell transplantation severe multiply organ failure against septic conditions developed due to almost complete absence of circulating white blood cells. RDS was accompanied by acute renal failure with unstable hemodynamics and hypoxic coma. After hemosorption condition has stabilized somewhat, body temperature decreased, urine output activated. Plasma exchange with replacement of 1.2 CPV proceeded without significant hemodynamic disorders. However, the persistence of deep leukopenia again activated septic inflammation and 2 weeks later again we had to repeat the same course of extracorporeal blood correction – hemosorption and plasmapheresis, after which the girl's condition finally stabilized, recovered consciousness, as well as adequate gas exchange and function of other organs.

This case shows possibility of success of extracorporeal detoxification and immunomodulation in extremely severe cases of septical complications not only in adults but also children, among whom were 3-6-month-old infants.

However, we should not wait for such a critical condition and perform adequate treatment in the early stages of sepsis when the negative dynamics of its development already emerges. Thus, it is necessary to take into account increase the severity of septical complications, fairly rapid in some cases, where just a few hours you can "lose" these patients.
**Disseminated intravascular clotting syndrome**

Disseminated intravascular clotting (DIC) syndrome is nonspecific general pathological process associated with the blood flow entering the blood coagulation and platelet aggregation activators, thrombin formation therein, activation and depletion of plasma enzyme systems, forming in the blood a plurality of cell aggregates and microclots, blocking microcirculation in organs, leading to the development thrombosis and hemorrhage, hypoxia, acidosis, malnutrition and deep organ dysfunction, intoxication of protein decomposition products and other metabolites, and often rise to secondary profuse bleeding.

These serious complications develop in obstetrics and surgery, septic shock and other critical and terminal states.

In the pathogenesis of DIC plays a leading role endotoxemia. As mentioned above, many biologically active substances such as structural components of endogenous intoxication, possessing membrane-tropic effect, violate the permeability of the vascular endothelium and contribute to toxic interstitial edema. However, equally toxic effects experienced by also cell components of the blood itself primarily platelets. Their excitement and increased aggregation ability promotes the release of serotonin and ADP and the formation of platelet microaggregates – the very first stage of DIC. Next, the process involved and the other links the blood coagulation system, passing stage primary hypercoagulable and then exhaustion complete failure. This is confirmed by the frequent development of thrombocytopenia in patients who are in critical condition. Thus, according to F.Stéphan et al. (1999), thrombocytopenia (less than 100x10^9/l) developed in 35% of patients being treated in the ICU with mortality in 38% of them, while it without thrombocytopenia was 20%. Risk factors for thrombocytopenia were sepsis, bleeding episodes and severity index of APACHE II more then 15.

The first stage of a hypercoagulable and intravascular coagulation accompanied microthrombosis and microcirculation disorders with nutrition disorders, tissue hypoxia and focal destructive processes. One of the "weak" and are vulnerable sites of the body is mucosa of the gastrointestinal tract, where start to form so-called ulcers stressor that for patients with severe pathology of the central nervous system are known as Cushing's ulcers, and in disseminated burns (over 70%) – Curling's ulcers. Such ulcers at up to 15-40% and often formed after heavy operations and trauma, shock and stress.

By the time of their formation (within 2-4 days of the critical state) phase hypercoagulable change anticoagulation and local destruction of the mucous
membranes exposed and damaged vessels, which creates prerequisites for the emergence of bleeding, which due to systemic hypo-coagulation may take profuse character with high (up to 40-60 %) mortality.

In the gastroscopy revealed the picture of the surface pattern of multiple mucosal erosions. Sometimes it is possible to note the signs of the syndrome Mallory-Weiss – cracks gastric mucosa. The rest of the bowel can also attack autolysis massive rejection of the villi and the growth of intoxication.

The mechanism of acute ulcers of the gastrointestinal tract associated also with the effects of local microcirculatory disorders occurring in sepsis and septic shock circulatory. Occurrence of vasospasm bowel, unrelated to the number of vital organs, first is physiologically justified. However, the converse recovery microcirculation is often delayed, leading to the development of hypoxic and ischemic tissue damage. Specific clinical studies of L.Oud and M.T.Haupt (1999), on 12 patients undergoing septic shock, showed that the pH in the bulk of the gastric mucosa is reduced from 7.33 after stabilization state to a total of 7.26 at 24 hours, 7.20 at 36 hours and remained reduced (7.24) after 48 hours. Thus, gastro-intra-mucous acidosis arose and persisted for at least 48 hours in patients even derived from septic shock, and did not depend on the normalization of hemodynamic, gas exchange and acid-base status in the bloodstream. All this undoubtedly contributed to the development of destructive processes in the mucous membranes, until the appearance of acute erosions and ulcers. The severity of these processes is confirmed by the fact that, despite the restoration of central hemodynamics and gas exchange, 10 (83%) of the 12 patients examined in the future still died.

For prevention and treatment of DIC used moderate systemic heparinization (up to 40-50 thousand units. daily) and glucocorticoids, infusion of dextrans and other colloids, introduction of trental and curantil. During profuse bleeding therapy – infusions of fresh frozen plasma, and in subacute and chronic forms of DIC – held plasmapheresis. Plasmapheresis removes activators of blood hemostasis, paracoagulation products, activated blood factors [Hanafusa N., et al., 2010; Solovyova I.N., Ragimov A.A., 2011].

It seems most reasonable pathogenetic holding massive plasma exchange, when along with the removal of toxic products is performed also replacement of fresh frozen donor plasma with all the normal components of hemostasis. The only way to break the vicious circles formed, do not give the possibility to eliminate manifestations of DIC. Donor plasma, as well as whole blood donation, with the introduction of an alone
without removing the factors that led to DIC, will be subjected to the same exposure to toxic substances, and such tactics can only delay the inevitable adverse outcome. On the other hand, a few hours after plasma exchange can observe a tendency to normalization of coagulation and bleeding stops. At the same time, should be resorted to plasma exchange without waiting for a complete picture of the unfolding of DIC with profuse bleeding. Such therapy should be preventive in nature and start at the first signs of impending complications – increased bleeding, identifying erosive changes of gastric mucosa and signs of coagulopathy, detected by laboratory study.

On the other hand, has already arrived in hemorrhagic complications permorm of plasma exchange is often pulled out of fear of increased bleeding during heparinization. Such tactics are dangerous because without liquidation the causes of DIC syndrome is almost impossible to eliminate it and excessive waiting is only the development of irreversible organ disorders.

In such cases, plasma exchange should be carried out without any use of heparin using conventional anticoagulant based solution of sodium citrate (ACD-A, CPD and the like). And even in cases where only the threat of bleeding, we use exactly the tactics extracorporeal anticoagulation system. It should be noted that even in critical situations, over 60% of plasmapheresis procedures performed using as anticoagulant sodium citrate solution only [Korach J.M.. et al., 2000].

**Acute 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 transdermal 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 (acetic acid poisoning, 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 the accumulation of toxic products and the suppression of the antioxidant system, decline in $\alpha$-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 devices kidney slows down as the primary damaging agent and the secondary products of disturbed metabolism. In particular, propylthiouracil, appointed at thyrotoxicosis can stimulate the formation of anti-neutrophil cytoplasmic antibodies (ANCA), can cause severe autoimmune vasculitis with pulmonary hemorrhage. In such cases, plasmapheresis provides a reliable therapeutic effect [Irani F. et al., 2009]. The same severe consequences observed in overdose fenprobarbats here also managed to stop them using plasmapheresis [Emet M. et al., 2009]. Plasmapheresis was effective in the treatment of acute liver injury in cases of poisoning tetrachlorethylene [Shen C. et al., 2011] and acetaminophen [Kondrup J. et al., 1992].

In practically all cases of poisoning application efferent therapy 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 [Luzhnikov E.A., Goldfarb Yu.S., 1995, 2005]. Severe organ disorders while contributing to the formation of products of "lethal synthesis", even more toxic than the primary xenobiotics. When hemosorption too, not all toxic compounds are removed sufficiently. In particular, in case of poisoning with psychotropic drugs tricyclic structure – antidepressants (imipramine, amitriptyline), antipsychotics (clozapine, azaleptin) and anticonvulsants (carbamazepine), plasmapheresis laundering erythrocytes was more effective than hemosorption. Plasmapheresis is effective enough in mushroom poisoning, amitriptyline, L- thyroxine, verapamil, carbamazepine, theophylline and heavy metals
E. Kolsal et al. (2009) also successfully taken out of amitriptyline poisoning old girl using plasmapheresis. 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 efferent therapy is most effective in the first 48 hours after mushroom poisoning.

No less serious consequences occur after snakebite. Thus, when viper venom poisoning develop severe endotoxemia with increased levels of leukocyte index of intoxication (LII) to 3.78 standard units, MWM to 0.49 standard units, 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 [C. Yildrim et al., 2006].

Nevertheless, the use also sorption methods of detoxification in the complex therapy of acute poisoning seems justified, as well as the application of oxidative- and photo-hemotherapy. Enterosorption will also contribute to slowing down absorption of exogenous product as primary and secondary enterogenous toxic compounds.

In acute poisoning, severe endotoxemia when accompanied by disturbances in membrane permeability of the endothelium with access from the vascular fluid and protein, hypoproteinemia, hypovolemia, impaired microcirculation, shows intense plasmapheresis reimbursement output volume native donor plasma. The total volume of plasma exchange may reach 1-1.5 CPV. Acute poisoning with thallium good therapeutic effect was achieved after cascade plasmapheresis [Tian Y.R. et al., 2005].

Timely delivery of efferent therapy can prevent the onset of irreversible organic disorders. Its beginning is possible both in the primary acute phase of poisoning, and in "light interval", which in most cases the primary stressor phase separates from the onset of multiple organ failure.

All of the above applies equally to cases of acute radiation and radionuclide lesions. In these cases hemosorbtion and plasmapheresis, both separately and combined, can significantly reduce the scale of the lesions, as well as secondary
metabolic and tissue disorders. While efferent therapy is indicated not only in the acute phase of injury, but in any long-term period, as even in fixed tissues radionuclides as heavy metal salts, can periodically go into circulation [Nechyporenko V.V. et al., 1997; Davydenko T.E. et al., 2003].

**Infectious diseases**

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.

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. Thus, activation of prooxidant and oppression of antioxidant systems is accompanied by accumulation of free radicals and toxic end products of lipid peroxidation [Shuvalova E.P., Antonova T.V., 1996]. Disturbances of hepatocyte membrane permeability contribute to the development of swelling last with intracellular acidosis and hypoxia. Damage of intracellular organelles, including lysosomes, accompanied by the release of powerful proteolytic enzymes (hydrolases) from necrobiosis of hepatocytes.
However, viral infection, particularly hepatitis B-virus, triggers a cascade of successive immunopathological reactions [Sorinson S.N., 1998]. Namely cytotoxic T-cells, forming the immune response are those effectors that perform cytolysis and death of the infected hepatocytes, mainly those which are contained in the virus antigen. Rapid immune cytolysis of hepatocytes often becomes the dominant factor in the pathogenesis of viral hepatitis. Furthermore, circulating immune complexes formed (antibody + antigen + C3 complement component) also causes adverse immunopathological reactions.

Especially dangerous is the fulminant form of hepatitis with massive liver necrosis, which was previously called "acute yellow atrophy of the liver" [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-lenticular 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].

Heavy 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 efferent 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 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 should be noted that in acute liver failure metabolism and inactivation of the sodium citrate is difficult, however, for these procedures, in spite of its potential toxicity this anticoagulant was used that nonetheless does not hinder the removal of patients from severe hepatic coma. The use of small doses of heparin allowed to dispense with the lower doses sodium citrate also. Sometimes requires removal of up to eight liters of plasma to adequately reduce the levels of ammonia, urea and amino acids, and cupping hepatic coma [Clemmesen J.O. et al., 2001].

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 LL 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].

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 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].

In *diphtheria* with severe endotoxemia, toxic myocarditis and autoimmune polyradiculopathy treatable with plasma exchange, held daily until stabilization of the patient’s condition against the background of indirect electrochemical oxidation of blood and the introduction of anti-diphtheria serum, which reduced the mortality rate from 66% to 6%. Plasma exchange allow not only prevent early, but later organ disorders [Vorobyev A.S., 1998]. A.S.Petruhin et al. (1998) also noted that the only way to influence the late neurological complications plasmapheresis is performed in the acute stage of the disease.

Of course, should be carried out and specific therapy with a special diphtheria antitoxic serum. However, the uncontrolled use of it may come a time when all the toxins in the blood, is completely bound and serum continues to be administered. This leads to accumulation of unbound antibodies which are deposited on the endothelium of small blood vessels, causing them damage and exacerbating manifestations of nephritis and myocarditis. Plasmapheresis can prevent such complications [Panchenkova N.R., Sokolov V.A., 1996].

Heavy cours develops as a result of infection caused by the *Epstein-Barr virus*, characterized by pancytopenia, coagulopathy, and liver failure. Besides immunosuppressive therapy, in severe cases it needs to turn to plasmapheresis [Abe Y. et al., 2010].

Severe intoxication accompanied and *tuberculosis* patients for which is also characterized by immunosuppression, further exacerbated during startup and long-term course of the inflammatory process. Indications for efferent therapy arise as in the period of preparation for surgery and in the postoperative period [Tityukhina M.V., 2012].

*Intestinal infections* has a definite value enterosorption preventing absorption from the intestinal lumen enterogenous and bacterial toxins. Severe poisoning was observed in some countries of Western Europe in the summer of 2011 caused by serotype O104:H4 *Escherichia coli*. Secreted with *Shiga-toxin* it causes severe enterocolitis with the development of hemolytic uremic syndrome, accompanied by high mortality. Antibiotics were powerless in this case or, on the contrary, contributed rise of endotoxemia. It became clear by the end of the epidemic, which forced to abandon antibiotics. Using plasma exchange the early stages of disease contributed to the rapid healing [Colic E. et al., 2011; Kreig L.S. et al., 2012; Ulrich S. et al., 2013]. J.T.Kielstein
et al. (2012), summarizing the experience of treating 631 patients in 84 hospitals in Germany, Sweden and the Netherlands came to the same conclusion. I. Yildrim et al. (2010) have been successful in the treatment of multiple organ failure on background thrombocytopenia induced *Salmonella enterica*.

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, 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 efferent therapy.

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].

Under these conditions, detoxification with removal of endotoxins and other pathological products allows to achieve a breakthrough in the course of the disease. The most effective kind of efferent therapy is plasmapheresis, which allows, in addition to removal of endotoxins, remove also all components incompetent humoral immunity. Replacement of the removed volume by donor plasma contributes to more effective protection and recovery more rapid and full recovery.

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.
It must be admit that at the present stage, these questions do not have considerable controversy and debate, and only weak material base and the lack of trained professionals holding back wider adoption of methods of extracorporeal detoxification, immune and efferent therapy in the practice of infectious medical institutions [Swedov A.K., Gurevich K.J., 1995].

I would like, however, to pay attention to much less studied problems postinfection rehabilitation as elimination of the main manifestations of infectious processes is still far from a full recovery of the affected organs and systems. In many cases, pathological toxic products that appeared during the main period of the disease, destroyed and removed simultaneously with the appearance of external signs of recovery. However, this does not always happen.

To the greatest extent it relates to viral hepatitis, when derivatives of bilirubin, bile acids, ammonia, products of lipid peroxidation and proteolysis continue to hold a "toxic press" hepatocytes, blocking them high enough potential to repair. This is the main prerequisite for the formation of chronic hepatitis and cirrhosis in the future with all the sad consequences.

Similarly, after the elimination of the main manifestations of diphtheria in the body are toxic products, autoantibodies and immune complexes, tropic to the myocardium, and toxic diphtheria autoimmune myocarditis completes eventually that did not have time at the height of diphtheria bacillus infection. In 50% of patients after diphtheria, observed neurological complications – late-type illness polyneuropathy like Guillain-Barre syndrome. Same rehabilitation may require also for patients who have suffered encephalitis.

In addition, after a series of infections formed almost real "acquired immunodeficiency syndrome" toxic origin with consequences no less serious than the particular viral AIDS.

All of this should cause the need for remedial courses efferent therapy mainly plasmapheresis, in early convalescence period. This primarily relates to hepatitis. Of childhood infectious diseases like measles and cunning differ scarlet fever, forming antibodies to the myocardium and the tropic of nephrons and mumps with gonadotropic effects. The danger is apparently harmless and rubella suffered by women before gestation or during the first trimester of pregnancy, which threatens to developmental defects of the fetus.
Guillain-Barré syndrome

This acute severe disease of the central nervous system, accompanied by progressive muscle weakness and paralysis, including respiratory muscles, which often require the long-term ventilation. In such cases, upon accession pneumonia, thrombocytopenia and bleeding, mortality can reach 12% [Netto A.B. et al., 2011]. At the basis of acute disseminated encephalomyelitis are demyelinating processes. Its connection with the chronic demyelinating diseases still debated, its pathogenesis is not clear, but the role of the immune system is undeniable. Often this process is preceded by viral infections and even vaccination, sometimes an infection caused by Campylobacter jejuni [Rogalewski A. et al., 2007]. At least 41% of patients identify this pathogen. Detectable acute disseminated encephalomyelitis connection with the transfer and on the eve of pneumonia caused by mycoplasma or bac. Legionella [Hagiwara H., et al., 2009; de Lau LM et al., 2010]. Detection of antibodies anti-ganglionic indicates a possible molecular mimicry between epitopes of the antigen of the infectious agent and the elements of the peripheral nerves, which determines the pathogenesis of this syndrome.

Previously widespread use of corticosteroids in Guillain-Barré syndrome has shown to be ineffective and was almost universally abandoned. Currently, the methods of choice are plasmapheresis and intravenous immunoglobulin, and often a combination thereof. One group of researchers [Plasma Exchange / Sandoglobulin Gullain-Barré Syndrome Trial Group, 1997] considered it appropriate immediately after plasmapheresis IVIG dose of 0.4 g/kg, which should block further production of antibodies. Total requires five plasmapheresis with removal of 50 ml of plasma per kg of body weight. Although J. Tharakan et al. (1990) considered sufficient removal of plasma total of 10-15 ml/kg daily until a stable effect and regression of disease. Another group [The French Cooperative Group ..., 1997 ] preferred plasmapheresis. The same tactic adopted and Quality Standards Subcommittee of the American Academy of Neurology [Hughes RA, 2011]. Japanese authors are of the opinion that plasmapheresis should be the method of choice in disseminated encephalomyelitis [Hagiwara H. et al., 2009].

Mild lesions (patients may undergo more than 5 meters without assistance) is just two sessions of plasmapheresis, with moderate (the patient can not stand without support) and severe (need for mechanical ventilation) is required for 4 sessions of plasmapheresis [Meena A.K. et al., 2011]. The same opinion is shared by J.C. Raphael et al. (1998), believes that the introduction of immunoglobulin for Guillain-Barre
syndrome is ineffective. In such cases, the plasmapheresis is preferred [Buzzigoli S.B. et al., 2010; El-Bayoumi M.A. et al., 2011; Hughes R.A., 2011]. It also describes and dramatic complications such therapy for the Guillain-Barré syndrome with intravenous immunoglobulin infusion at a dose of 0.4 g/kg body weight – the development of severe acute allergic myocarditis with death [Koehler P.J., Kondstaal J., 1996]. In the treatment of severe forms of the disease in children is more effective plasma exchange, but the technical difficulties of plasmapheresis in these patients are forced to use medication.

However, recent studies show a lower efficiency of immunoglobulin therapy compared with plasmapheresis [Dada M.A., Kaplan A.A., 2004; Lin C.H. et al., 2004]. In addition, the cost of five infusions of immunoglobulins is $10.329.85, while the cost of five sessions of plasmapheresis twice smaller – $4.638.16 [Winters J.L. et al., 2011].

It was possible to extract IgG and IgM autoantibodies, obtained by passing through the plasmapheresis plasma column with covalently fixed Trp (immunosorption) [Haupt W.F., 2000]. Favourable results were obtained using techniques cascade plasmapheresis [Valbonesi M. et al., 2001]. However, when analyzing the results of using plasma exchange rates (3 liters per session) and cascade plasma filtration, the latter benefits were not found [Lyi R.-K. et al., 2002].

**Critical care in obstetrics**

**Ovarian hyperstimulation syndrome** develops in the treatment of infertility in order to increase the number of mature follicles and ovulation stimulation using anti-estrogens, and gonadotropin agonists "gonadotropin releasing hormone." Among the most serious consequences of this syndrome describe severe endotoxemia with increased vascular permeability, hypoproteinemia, hypovolemia, hemoconcentration, leading to the appearance of ascites, hydrothorax and hydropericardium, as well as the development of hypercoagulability and thromboembolic multiple major vessels until death.

Frequency abortion this background is 29%, and premature birth – 44%. 62% of neonates are born underweight. 13% of pregnant women against this background develops hypertension, at 5.9% – preeclampsia, at 4.4% – gestational diabetes, 4% discontinuities or placental abruption arise. 44% of pregnant delivered by caesarean section [Abramov Y. et al., 1998]. Attempts to prevent the development of this syndrome with the introduction of massive doses of albumin at the time of egg retrieval or immediately after proved were unsuccessful [Ndukve G. et al., 1997]. And so far the most radical method of treatment is an emergency interrupt long-awaited pregnancy.
At the same time, the use of therapeutic plasmapheresis in the development of ovarian hyperstimulation syndrome in most cases can cut its manifestations. In order to prevent this complication in preparation for in vitro fertilization and background as pregnancy and appropriate use of therapeutic plasmapheresis, able to reduce the activating effect of superovulation on the hemostatic system and create more favorable conditions for the process of implantation and subsequent development of the embryo.

**Bleeding.** Prevention of bleeding remains one of the most pressing problems of obstetrics. Their frequency ranges from 2.7 to 8% of the number of labor. In pregnant by the end of III trimester of pregnancy there is a pronounced hypercoagulable by increasing the activity of clotting factors – increasing the content of fibrinogen, platelet aggregation, lowering blood fibrinolytic activity. These processes are most intense in the presence of antiphospholipid syndrome in pregnant women [Demina T.N. et al., 2004].

Development of DIC often occurs during labor complicated by bacteremia with the spread of infection from the birth canal, or with infected amniotic fluid. Amniotic fluid embolism, even in the absence of infection, also often leads to the development of DIC and the profuse bleeding. This contributes to preeclampsia and premature detachment of the placenta, and intrauterine fetal death.

Abruptio placenta is one of the leading places in the structure of maternal and perinatal mortality. The main reason for such a premature placental abruption is late preeclampsia (51.9%), and perinatal mortality in such cases reaches about 21.9% [Demina T.N., 2004].

Without going into the details of the treatment of bleeding already arisen held by all the canons of Hemostasis and Transfusion medicine, focus only on measures to prevent them.

In all cases, the main motivating factor for the occurrence of DIC and placental pathology is the accumulation of substances with excitation membranotropic platelet aggregation, as well as disorders of the placental circulation. Therefore, all of the above methods of efferent therapy of preeclampsia and other endotoxicosis serve prevention such bleeding also. Nevertheless, and iso-coagulation not typical for this gestation period, and the high risk of bleeding during childbirth O.V.Rogachevsky et al. (2005) for the correction of the hemostatic system is considered the method of choice plasma exchange, which allows to significantly increase the blood coagulation potential, improve microcirculation and tissue nutrition. In 15 of these patients using plasma exchange (removed plasma was replaced 1:1 by fresh frozen donor plasma) succeeded
Eclampsia. Increase in the severity of late toxicity (preeclampsia) before birth in some cases dictates the urgent need to abort the pregnancy regardless of the fate of the baby, as eclampsia, as the apophasis of preeclampsia, threatens toxic brain edema (coma, convulsions, retinal detachment), a toxic edema of lung parenchyma with severe respiratory failure, nephropathy until anuria, liver failure (bleasotes, acute yellow atrophy of the liver). Each of these complications, not to mention their combined one-stage, threatens the life of the mother and requires the most urgent measures for intensive therapy. Thus the most reasonable pathogenetic solution is detoxification and efficient therapy, undertaken in prenatal, provides a more favorable environment for future childbirth, and even for emergency delivery, which create additional and significant burden on the major organs and systems. In addition, we can not exclude the possibility of prolonging pregnancy in its early timing, although it should be recognized that the fetus while already in extreme conditions of existence for quite some time and complete recovery of his health at the time of delivery is a major challenge. This is particularly true for hypertensive disorders of pregnancy, which can significantly reduce mortality [Serov V.N. et al., 2005].

However, against the background of already some complications, performing therapeutic plasmapheresis prevents the onset of more severe complications. At the same time, plasmapheresis should begin as early as possible, as continued circulation thromboplastic factors in the bloodstream can cause repeated hemostatic disorders. Plasmapheresis on a background of generalized hemorrhagic syndrome with decreased levels of prothrombin less than 50% and increased bleeding on the injection site within the first 12 hours after the onset of bleeding can significantly reduce mortality [Serov V.N. et al., 2005].

It should be borne in mind that in the context of anticoagulation membrane plasmapheresis can be carried out completely without heparin using a solution of sodium citrate.
emphasizes the need for timely preventive detoxification and efferent therapy throughout pregnancy and even before her.

In the postpartum period efferent therapy aimed at restoring health, and sometimes exclusively on resuscitation of the mother. The effectiveness of these measures depends on the time of their inception. Given the need for anticoagulation and risk cause or exacerbate bleeding, the earliest date for such procedures after delivery or cesarean section is 6 hours. The complex of these measures may conduct hemosorption, plasmapheresis, plasma exchange, plasma adsorption, ultrafiltration, photo-hemotherapy and indirect electrochemical oxidation of blood.

Volume and a combination of these procedures depend on the type and degree of homeostasis disorders, organ failure. Plasmapheresis, performing against the backdrop of preeclampsia in the postpartum period helps to reduce the level of endotoxemia, restore diuresis, lower serum creatinine, bilirubin, transaminases, to normalize coagulation [Serov V.N. et al., 2005, 2011].

Our own experience of these events shows that detoxification contributes much more rapid reconstitution of the affected organs than traditionally held therapy – medication, infusion, artificial ventilation, and even hyperbaric oxygenation. In particular, diuresis, even against complete anuria, may recover for the past hemosorption as removing “toxic press” of the kidneys, and in the next few hours there is a restoration of consciousness and airiness of the pulmonary parenchyma. Belated detoxification shows a delayed inverse dynamics of organ damage.

However, in one case, even after four weeks of deep coma after eclampsia, on a background of severe RDS, anuria and hydrops, hemosorption with ultrafiltration (2.5 L) resulted in the restoration of elements of consciousness the next day, re-hemosorption with ultrafiltration achieved full recovery of consciousness, renal function, lung airiness, and only demanded more bedsores long follow-up treatment.

One of the causes of severe multiple organ failure in the postpartum period is amniotic fluid embolism, when the uterus gets gaping vessels enter liquid containing not only urea and meconium, but also pieces of chorion. Heavy toxic cerebral edema, pulmonary edema, and microemboli with disorders of the central hemodynamics and microcirculation can also be recovered using hemosorption and plasmapheresis. In our practice, when one of these cases needed and prolonged extracorporeal membrane oxygenation for 24 hours with three consecutive sessions of hemosorption, which also led to the complete restoration of the affected organs.
Intra-hepatic cholestasis of pregnancy often complicates the second half of pregnancy and is accompanied by intense pruritus, intensifying at night with sleep disturbances, nausea and vomiting. The examination revealed a 5-10-fold increase in transaminase levels, 2-3-fold increase in direct bilirubin, total alkaline phosphatase, thymol indicators, 10-100 times increase in the content of bile acids (most of cholic, chenodeoxycholic less). In cholestasis very often develop preeclampsia (87%), the threat of miscarriage (65%), preterm delivery (35%) with a syndrome of intrauterine fetal growth retardation (29%), chronic fetoplacental insufficiency (87%) with perinatal mortality, reaching 15% [Lineva O.I. et al., 2000].

These disorders are resistant usual therapeutic measures and are often forced to prematurely terminate the pregnancy. In this regard, there are indications to eliminate toxic substances through efferent therapy. N.V.Deryabina et al. (2003) reported the first experience of using membrane plasmapheresis courses in 30 patients with cholestasis gestation 26-35 weeks. Decrease of pruritus was noted after the first session of plasmapheresis, improved sleep and appetite.

The normalization of bilirubin, a threefold reduction in transaminase levels, a significant decrease in alkaline phosphatase and diene conjugates with normalization of antiradical activity. In all cases, a full-term pregnancy was prolonged up to date. In the control group, despite the use of hepatic, antioxidants and other drugs continued to increase bilirubin, transaminases and alkaline phosphatase in the blood, which was accompanied by the deepening of hypoxia and fetal malnutrition, placental insufficiency. This led to the premature birth or early termination of pregnancy, weakness tribal forces with greater frequency of cesarean section and increased risk of fetal death. Positive results of treatment of cholestasis with courses of plasmapheresis have A.V.Nikolaev et al. (2005). A. Mathias et al. (2009) also consider the use of plasmapheresis justified in such cases.

Acute fatty liver of pregnant - more severe pathology associated with a high risk of neonatal and maternal morbidity and mortality. It often develops and DIC with massive bleeding. With slightly better outlook also takes frequent complication of late pregnancy HELLP-syndrome (hemolysis, elevated liver enzymes, low platelet syndrome). In these cases often develop hemolytic anemia and thrombocytopenia with high perinatal mortality. Genesis of these complications lies in genetically related disorders free fatty acid oxidation fetus [Ibdah J.A. et al., 1999]. However, the complex
can be traced with the appearance of autoimmune disorders autoantibodies placental tissues and liver lipoprotein lowering background amount and regulatory CD4\(^+\) and CD25\(^+\) T-cells [O.P. Tan'ko et al., 2006]. Given the high risk of fetal death, premature detachment of the placenta and bleeding during childbirth expedient to intensive plasmapheresis with removal of up to 50% CPV and replacement of fresh frozen plasma donation [Padden M.O., 1999; Förster J.G. et al., 2002; Eser B. et al. 2005; Bayraktaroglu Z. et al., 2006; Nasa P. et al., 2011]. It is emphasized that the outcome of thrombotic thrombocytopenic purpura without plasma exchange is almost always fatal [Myers L., 2010].

**Hemolytic uremic syndrome** in the postpartum period is often accompanied by HELLP-syndrome, and also leads to a high mortality. Emergency plasma exchange, made in the first 24-49 hours after its detection can prevent an adverse outcome [Dixit S. et al., 2012].

**Purulent-septic complications.** The frequency of postpartum infectious complications as high as 26%. Among the reasons was high on amniotic infection (chorioamnionitis or) to infection by amniotic fluid, chorion, placenta [Novikova O.N. et al., 2000 ]. The part of obstetric sepsis of maternal mortality rate is 37-39%, mainly due to progressive damage to the major vital organs – lungs, liver and kidneys. It should be noted a significant increase in lipid peroxidation products with inhibition of antioxidant defense system in parturients with purulent complications [Dolgoshapko O.N., 2006].

Because pregnancy itself is accompanied by physiological immunosuppression, which may be exacerbated as a result of toxicity, it is possible aggravation dormant infectious processes, among which the leading role has pyelonephritis. It can, on the one hand, sharpen and deepen preeclampsia during endotoxemia, on the other hand – increase the risk of intrauterine infection of the fetus, so the fight with pyelonephritis becomes important and not the last place here should take therapeutic plasmapheresis and photo-quantum therapy [Novikov O.N . et al., 2000; Dolgoshapko O.N., 2006].

In the postpartum period there is in the forefront risk of **endometritis**, which may be accompanied by sepsis and septicemia. The severity and lightning during endometritis caused also abundant vascularization and large suction surface of the uterus endometrium. Under these conditions, only the timely removal of circulating shock-metabolites, excess inflammatory mediators and fibrinolysis products using plasmapheresis can turn the tide of the disease, reduce the time of hospital stay from 42.4 to 24.6 bed-days, length of intensive care from 29.2 to 8.4 days and reduce
maternal mortality from 64% (in the comparison group) to 15.6% in the group of women in childbirth, which is a comprehensive treatment was carried out in the early stages of sepsis [Dolgoshapko O.N., Chermnykh S.V., 2008]. Many authors emphasize that the efferent therapy should be started in the first hours of septic shock.

At the first stage of treatment is most expedient hemosorbtion indirect electrochemical oxidation and ultra-violet irradiation (UVI) of blood, and then plasma exchange sessions when removed from plasma immune non-competent elements replaced native donor plasma containing immunoglobulins, antibodies, complement, opsonins capable of immediately come to grips with pathogens. UVI of blood and plasmapheresis conducted during pregnancy about preeclampsia, reduce the risk of septic complications after cesarean section [Ivannikov N.F. et al., 2000].

V.V.Vetrov et al. (2003) reported on the experience of using hemosorption, plasmapheresis and blood UVI 124 postpartum women with postpartum infections (pyelonephritis, metro-endometritis) with good clinical effect, allowing you to reduce the dose of infusion and antibacterial agents, and their hospital stay was 3-5 days less compared with a control group of similar patients. These results allowed us to move to a prophylactic plasmapheresis and blood UVI 64 postpartum women at risk of developing postpartum infections. In these cases, the outcome of the post-partum period was favorable in all women with improved health, lactation, involution of the uterus, biochemical and clinical blood tests. Every fourth patient was cured without any antibiotics [Vetrov V.V. et al., 2000]. Preventive holding plasmapheresis prevents the development of multiple organ failure [Jojua T.V. et al., 2009; Meshalkina I.V., 2011].

The same tactics efferent therapy of septic complications and is used in gynecological practice in endometritis after illegal abortions, pelveo-peritonitis etc. In some cases, it is timely detoxification can cut acute inflammatory process and avoid hysterectomy have more young and nulliparous women. In addition, plasmapheresis can cut menstrual irregularities and uterine bleeding during chronic inflammatory diseases of the pelvic organs in girls [Nemchenko O.I. et al., 2004].

Considered rational conduct preventive efferent therapy at the planning stage of pregnancy, which helps to improve the clinical status of patients with increasing inter-recurrent period 2.9 times, reduction in the severity of prodromal symptoms in 3 times, improving the body's detoxification function, which should provide more favorable for future pregnancy [Fedorova T.A., 2003].
Neonatology

As noted above, serious complications pre-, intra- and post-natal periods lead preeclampsia, accompanied by the same toxemia, fetal intrauterine hypoxia, exacerbated its consequences exacerbations of chronic urogenital infection and rhesus-conflict mother and fetus.

These complications are the main causes of fetal death. They contribute to premature birth, in which even born alive, the baby is in critical condition with a complex multiple organ disorders, can not be corrected with the help of any artificial or assisted ventilation with oxygen or hyperbaric chambers, no antibiotics or any other medications.

This is because in the circulation, interstitium and cells of the body are found in a huge variety of toxic products that do not give way to restore normal metabolism of organs and tissues with the development of a series of vicious circles. Toxic press makes it impossible to establish a normal hepatocytes, alveolocytes, neurons, renal parenchyma, which delays the recovery of natural detoxification processes, excretion and gas exchange. Break these vicious circles without removing of toxic products is almost impossible, which explains the significant incidence of early neonatal mortality and allegedly recovered child is doomed from childhood remain chronically ill, suffering from liver disease until cirrhosis, kidney, lung, and various manifestations of allergy and immune shifts, which differ little from the acquired immunodeficiency syndrome, ie actually AIDS. The frequency of disorders of the nervous system in newborns of their mothers with preeclampsia reaches 15%. Most often it is hypoxic and ischemic damage with subsequent disability children. This encephalopathy is a consequence of severe metabolic disorders in the brain tissue, a kind of "metabolic catastrophe" [Kulakov V.I. et al., 1998]. Perinatal cerebral hypoxia remains one of the most common causes of chronic subsequently developing neurological disorders, mental retardation and even epilepsy [Vannucci R.C., Perlman J.M., 1997].

Intrauterine growth retardation affects the subsequent growth of the child. Such children have greater incidence of mortality and morbidity with a higher frequency of cardiovascular disease, hypertension, hyperlipidemia, diabetes mellitus type 2 and other endocrine disorders, leading to their premature death as an adult [Celsi G. et al., 1998]. Although about 80% of these children in the first 6-12 months of catching up in its development of "full-length" peers, but others remain smaller growth in childhood and in adulthood, their growth is also less genetically predetermined in their families. Among the factors regulating fetal growth plays an important role "Insulin-like growth factor,"
which not only stimulates the proliferation of cells of the fetus, but also affects the
distribution of nutrients between the placenta and the fetus toward the latter [Cianfarani S. et al., 1998].

One of the most serious complications in newborns, especially premature, are lung
disease – **respiratory distress syndrome** that develops not so much due to the
immaturity of the surfactant system of the lungs, but because of toxic lung injury in an
adult type of RDS. This occurs due to severe neonatal endotoxemia in a wide range of
complications during pregnancy their mothers – eclampsia, intrauterine infections,
autoimmune disorders of pregnancy, which lead to premature birth. This is confirmed by
studies in St. Petersburg Pediatric Medical Academy [Evtyukov G.M., Ivanov D.O.,
2005].

Naturally, such complications is easier to prevent a timely spending detoxification
of pregnant with the threat of intrauterine hypoxia, but after the birth of excretion of toxic
products from the circulation should help more rapid and full recovery of brain and other
vital organs of the newborn.

Serious problem is the **meconium aspiration syndrome**. Last appears in the
intestines of the fetus to the 20th week of gestation, its passage in the amniotic fluid
occurs for the 37th week, although pathological pregnancy find it there much earlier. If
you have complications of fetal hypoxia occurs with its hyper-peristalsis bowel and
easing its sphincters, which promotes the release of meconium in the amniotic fluid, on
the one hand, and on the other – are excited fetal breathing movements and opening
his glottis. Inhalation of meconium leads to airway obstruction, distelektasis, violation of
ventilation-perfusion relationships. There are cases when meconium aspiration
combined with intravascular coagulation of blood in the veins and arteries. Meconium
promotes pneumonitis, hyper-inflation airway, local areas of emphysema,
pneumomediastinum and pneumothorax, early septicemia, pulmonary hemorrhage and
thrombosis massive pulmonary and systemic vascular microcirculation [Sergi C. et al.,
1998]. Treatment of this complication is an extremely difficult problem, which once again
underlines the usefulness of normal conditions of fetal development through efferent
therapy of pregnant when there is suspicion of pathological course.

Often develop **septic complications** in newborns also. Every year they occur in
30 million infants and 1.2 million of them die [Afroso S., 2006; Zaidi A.K.M. et al., 2011].
Even in developed countries, their number reaches 520.000 and no tightening of the
rules of hygiene or antibiotics are not always able to cope with them and at the same
mortality as high as 40% [Blencowe H. et al., 2011].
In recent years, an increasing number of reports of such specific complications of early period after birth, bronchopulmonary dysplasia (BPD). Virtually unknown 10-20 years ago, now it is a complication of a leading place among the causes of lung diseases in children. In the United States are diagnosed each year up to 7000 such cases. Most often develops in the BPD artificially ventilated preterm infants. Mechanical ventilation and oxygen therapy increases survival of premature infants, but the risk of developing BPD is on the increase. Underdeveloped lungs, barotrauma, and oxygen toxicity, increase in pulmonary tissue cytokines (IL-1, IL-6, IL-8), molecules "intercellular adhesion", macrophage inflammatory proteins are the main etiological factors of complications [Singer L. et al., 1997; Thome U. et al., 1998].

BPD may develop in 20% of infants who received mechanical ventilation. Children with BPD have a higher risk of death in the early period after birth. But after discharge, these children have a higher risk of frequent respiratory diseases, growth disorders, cardiovascular disease and neurological disorders. The risk of developing BPD does not always depend on the severity of respiratory distress in newborns. Meaning of intrauterine infection is confirmed by finding fetus microbial invasion of the amniotic fluid in 25% of premature babies. It is often associated with the presence in the liquid of proinflammatory cytokines such as IL-1β, TNF-α and IL-8. These microbes, cytokines and other biologically active substances can be aspirated during fetal breathing, lead to intrauterine pneumonia, making the lungs more susceptible to barotrauma and oxygen toxicity with increased risk of BPD [Yoon BH et al., 1997].

There is threat to the health and even the life of the newborn alloimmune thrombocytopenia creating, developing as a result of crossing the placental barrier in the event of autoantibodies mother her "gestational" thrombocytopenia. Decrease in number of platelets to her 80x10^9/l is not yet accompanied by what or clinical symptoms or even significantly increases the risk of bleeding during childbirth. However, neonatal alloimmune thrombocytopenia can lead to serious complications in the newborn, especially in disorders of childbirth fraught with intracranial hemorrhages. For the prevention of neonatal bleeding even attempted intrauterine platelets transfusions [Greaves M. et al., 1997]. Although, of course, more rational in such cases it would plasmapheresis in a pregnant suspected of such autoimmune thrombocytopenia.

You should consider a limited use of exogenous surfactants, because, as noted in the above-mentioned special studies (see "Pathogenesis of respiratory distress syndrome"), in the presence of toxic pulmonary edema and penetrate the alveoli products that inhibit not only natural, but input from outside surfactant that practically
negates the effectiveness of such therapy. Without excluding the possibility of its implementation, it seems to us that the first thing you want to stop entering of such inhibitors of surfactant in the alveoli by reducing the permeability of the vascular endothelium, achieved detoxification using plasmapheresis. In such cases may not require use of exogenous surfactant, since the normalization of metabolism of the lung parenchyma, including type II in alveolocytes, reproduction of necessary surfactant amount is reached in a few hours. This was confirmed by our own experience of plasmapheresis in very preterm infants, when X-ray examination a day after such a procedure is almost restored airiness and pulmonary gas exchange with the normalization of their functions.

All the above facts indicate the vital need for emergency normalization of the internal environment of newborns.

Our method syringe membrane plasmapheresis with plasmofilter PFM [Voinov V.A. et al., 1996], made it possible to carry out the efferent therapy newborns, including premature weighing from 700 g. Indications were complications by intrauterine infection and sepsis, consequences of severe asphyxia, hyperbilirubinemia soil hemolytic disease of the newborn [Polyakov S.Z. et al., 1995]. M.A.Vyugov et al. (2003) reported a significantly more pronounced decrease in the dynamics of bilirubin and hemolytic disease of the 23 newborn after syringe membrane plasmapheresis. Syringe method plasmapheresis also been successfully used in the treatment of 33 babies with the syndrome of endogenous intoxication, hemolytic disease (29) and septic complications (4) [Zauralskiy R.V. et al., 2004]. The same results in the treatment of hyperbilirubinemia in neonates using membrane plasmapheresis were achieved Yu.A.Batman et al. (2009) in Donetsk (Ukraine).

Given the severity of the babies with significant disorders of circulatory dynamics and gas exchange, plasmapheresis operation required careful to maintain the constancy of the blood circulation volume and general body hydration. Plasmapheresis was carried out in a synchronous plasma exchange to the completion of an equal volume of plasma removed by donor fresh frozen plasma or native with replacement 1-2 CPV, which led to a significant decrease in the degree of endotoxemia with the normalization of clinical and laboratory parameters. This ensured a reduction of time spent in the ICU by 25% in generalized infections and septic complications and 6.7% with severe asphyxia. Mortality in these groups decreased by 35.3% and 5.7%, respectively. Also was decreased time finding children on mechanical ventilation, need sympathomimetics infusion, time of enteral nutrition beginning [Polyakov S.Z. et al.,
1995]. Positive results using plasmapheresis in purulent-septic diseases of newborns were obtained by other authors [Mirlas M.F. et al., 2005].

Admittedly that timely membrane plasmapheresis babies in critical condition can be rather efficient way to prevent also above bronchopulmonary dysplasia and other complications detected at a later stage of the development of children.

It should be noted that indications of efferent therapy should occur not only in critical conditions, but when the immediate threat to life of the newborn is not. Transferred endotoxemia and intrauterine hypoxia, especially in prematurity when the causes of preterm birth is the phenomenon of preeclampsia or intrauterine infection, undoubtedly accompanied by significant violations of the internal environment. Only removal of pathological products from the body can create conditions for full recovery of most of the functions, correct structural tissue disorders, metabolism and immunogenesis. Essentially, each premature baby is significant disorders of homeostasis, because the very fact of premature birth involves a complicated pregnancy with the accumulation in the body, both the mother and fetus of a number of pathological metabolites. In these cases, it may well go about preventive efferent therapy, in which also lies plasma exchange. Removing pathological products of the internal environment of a premature baby can be "lifted" from his "dark and musty basement " on the mezzanine light and thus create a higher starting level for its further development and life.

**Efferent therapy in pediatric critical states**

Indications for efferent therapy not less also in children early months and years of life. This severity of inflammatory diseases of the lungs and abdominal organs due to deficiency of the immune system even in infants [Mironov P.I. et al., 1995]. There are also infectious diseases, including hepatitis, diphtheria, intestinal infections, etc. Plasmapheresis promotes more rapid relief of manifestations of diffuse purulent peritonitis [Razheva I.V. et al., 2002] and acute liver failure [Singer A.L. et al., 2001] in children. Plasmapheresis with UV blood irradiation was effective in the treatment of secondary purulent meningitis complicating purulent sinusitis and mastoiditis. When hemolytic-uremic syndrome, plasmapheresis was more effective than hemodialysis [Georgaki-Angelaki H. et al., 2011].

Use of plasmapheresis in children's hospitals in the United States over the last ten years has increased, especially in thrombotic thrombocytopenic purpura, myasthenia...
and Goodpasture syndrome. In addition, in children as well as adults, indications for efferent therapy occur when poisoning, burns, injuries, etc. [Sussmane J.B. et al., 2012]. Furthermore, among the indications for plasmapheresis in children pointed pneumonia, sepsis, disseminated intravascular coagulation, meningitis, allergies and autoimmune diseases.

It should be noted some technical difficulties of plasmapheresis in children associated both with low weight of their bodies, and with restrictions on the use of their vessels. Not every device can be used in pediatric practice. However, the following domestic plasmofilter "Rosa" and portable device "Hemofeniks" are quite suitable for use in children, even very young age [Voinov V.A., 2010, 2013].

Membrane plasmapheresis

Analysis of all the above material convincingly demonstrates the validity of using efferent therapy in the treatment of many diseases, both acute and chronic. Of all the methods of efferent therapy the most effective is plasmapheresis, and techniques of the last membrane plasmapheresis was not only the physiological, but also more affordable in the practice of the widest network of medical institutions. It's noted also in the analysis of the use of membrane plasmapheresis in 20 years in the U.S. [Siami G.A., Siami F.S., 2001]. There are emphasized greater simplicity and safety, lower blood trauma as well as loss of platelets and leukocytes, as compared to centrifuge techniques. In Japan, preference is also given to membrane technologies, considering centrifuge machines more cumbersome and expensive [Kawamura A., 2003].

Nevertheless, membrane plasmapheresis was the least coverage in the Russian medical literature. Hemosorption subject of several capital works [Nikolaev V.G., 1979; Lopoukhine Y.M., 1985], as well as gravity-centrifuge plasmapheresis [Gavrilov O.K., Gavrilov A.O., 1995]. This gap to some extent was filled in our monographs ("Efferent therapy. Membrane plasmapheresis"), published in 1997, 1999, 2002, 2006 and 2010.

Numerous firms abroad («Gambro», «Fresenius», «Cobe», «Dideco», «Terumo») followed the path of development and production plasmafilters based porous hollow fibers. This is a fairly complex technology, providing the creation of highly functional, but costly membrane devices. If for hemodialysis able to reduce production costs and bring the price of dialyzers to 15 U.S. dollars, the cost plasmafilters remains more than $ 100, reaching $ 250. To this we must add that each of these requires a set of disposable plasmafilters highways cost $ 10-15.
In addition, firms producing plasma filter, and create their own devices, costing from $25,000 to 100,000, without which it is impossible to carry out the operation membrane plasmapheresis. Therefore, by purchasing one of these devices with the primary set plasmafilters we "for life" become slaves to the firm, which are forced to continue purchasing plasmafilter and all other supplies from the same company or this unit remain a monument of funds spent and frustrated hopes. All this taken together makes it virtually unattainable in the use of imported plasmafilters in Russia.

Attempts to manufacture membrane plasmafilters based porous hollow fibers in Russia, copying foreign models have failed, mainly because of the lack of appropriate domestic industrial technology and materials. More productive was the idea of creating plasma filter using flat porous, so-called track membranes developed by a team of scientists of the Joint Institute for Nuclear Research (Dubna) and the Institute of Crystallography (Moscow) under the leadership of the G.N.Flerov.

They were prepared by bombardment of argon nuclei in the subsequent etching with the accelerator in an alkaline solution. In those places where has such a kernel traces (trace in English track, hence the name of the membrane) with the destruction of material and etching are formed there is round the same pore size of which depends on the concentration of the alkaline solution and the exposure time. The first such plasma filter PFM-800 has been approved for clinical use in 1992.

Basis of the device is a flat porous track membrane lavsan thickness of 10 microns with a pore diameter of about 0.5 microns, which allows you to freely pass through all the recent liquid blood components and detain all formed elements.

By 2000, the domestic company "Trackpore Technology" started not only to develop a new plasma filter, but also to build a complete industrial cycle production in CPA "Alpha" in Dubna, Moscow region. For this was made own nuclear accelerator "bombing" of the membrane, pickling plant for pore formation and assembly shop plasmafilters. At present, this company is the only producer in Russia plasmafilters (patent number 2156156 from 20.09.2000) and apparatus for membrane plasmapheresis, meet all requirements GMP and other relevant international standards that allowed us to obtain in 2011 the EU-certified quality (CQ-102011-II on the apparatus "Hemofeniks" and RQ-102741-II in the plasma filter "Rosa" with a set of lines, CE-0535) and is currently undergoing a phase of active their introduction in many countries of Western Europe, India, China and others. This was facilitated by the qualities of the machine, as its portability, simplicity and security, small filling volume of the extracorporeal circuit, which distinguishes it from many foreign models.
Methods of membrane plasmapheresis. Such a set of indications for plasmapheresis in a variety of clinical situations – from intensive care to outpatient therapy, from neonatology to gerontology, implies different methodological approaches to the conduct of such operations. There are three groups of methods of membrane plasmapheresis with plasmafilter "ROSA".

The first group – manual plasmapheresis, because it does not require any of the pumps and devices, and the blood is taken from the patient and passed through the plasmafilter under the action of gravity only. The second method – syringe plasmapheresis for infants and young children. Third – using small single-needle devices series "Hemofeniks."

Each of these methods has its own characteristics, advantages and disadvantages, making them preferable for certain clinical situations. For each of them is available and appropriate system of highways complete with plasmafilter "ROSA".

Single-needle manual membrane plasmapheresis. To ensure the implementation manual membrane plasmapheresis required basic conditions of the treatment room and regular transfusion bedside stand, which is fixed with a special bracket plasma filter, and infusion set socket rack bottles with solutions. The basic principle of operation consists in taking blood from the patient and its passage through the plasma under the action of gravity only. The system works at three phase.

Initially moved dissolved sodium citrate and sodium chloride in the bag for the collection of blood in a dose required for anticoagulation and rheology in accordance with the selected method.

When the second phase is taken into the blood bag to collect it, bypassing the plasma filter.

At the third phase, after the package is full of blood it is moved to the top position and open the way through the plasmafilter returning it in the same vein. And during this period the plasma is separated. During return of the thickened blood its may synchronous dilution isotonic sodium chloride solution or other plasma expanders (up to donor plasma).

The simplicity and safety of this method allow its use not only in health care facilities, but also in the military field hospitals and mobile division in the aftermath of natural disasters [Popov A.S. et al., 2007].
Single-needle syringe plasmapheresis in children. Use in neonatal intensive care, particularly preterm, conventional methods of detoxification — hemosorption and gravitational (hardware or batch) plasmapheresis encounters a number of formidable technical and methodological difficulties, the main ones are: low body weight, and, respectively, low blood volume, hemodynamic instability, very sensitive to the deficit CBV; deficit "vascular capital" of babies not allowed to use a catheter diameter 0.6-0.8 mm, long catheters same finding in umbilical vessels fraught with thrombosis in the portal system, septic complications.

Practically all known methods using different devices (including for membrane plasmapheresis) foreign firms have a very significant amount of filling, comparable to child CBV, and are designed for perfusion rate exceeding capabilities of small vessels and catheters.

Methods used to practice portions of the blood sampling syringe to 20 ml followed by centrifugation and removal of plasma and the return of the thickened or diluted blood is very tedious and prolonged (4-6 hours).

No less difficulty plasmapheresis and the first months and years of life with a body weight of 15-20 kg, when the intake of blood units did not allow for more than 100-150 ml, which also does not allow full use of the most common methods of batch centrifuge.

Membrane plasma filter PFM was the most fully meeting all requirements for plasmapheresis in newborns (including premature) and young children, because it has the minimum amount of own filling (no more than 15 ml) and can be used without any devices using only one syringe for single-needle technique [Voinov V.A. et al., 1996]. The work comes three phases. During the first phase a syringe filled with anticoagulant solution or donor plasma. At the second — blood is drawn from the vein of a child through the venous catheter. During the third phase the syringe pumps blood mixed with anticoagulant in the plasmafilter and then returns it to the same catheter. And during this period, the plasma is separated.

Since the variable blood volume does not exceed 4-8 ml, and plasma separation occurs gradually, this technique easily tolerated by children, even in a critical condition and with hemodynamic instability, including premature infants weighing from 700 g

Single-needle membrane plasmapheresis on a portable device "HEMOFENIKS." The basis of the device is the chamber pump "ventricles" type with inlet and outlet valves, which in the period of "diastole" blood is passively drawing from
a vein, and during "systole" send it to the plasma filter, then return into the same vein. For this device have been set up for external clamping tubes, synchronized with the phases of the cycle – the suck and return the blood. Pressure in the plasma filter is registered directly in the blood stream before it by the sensor separated from the line hydrophobic filter. Given the current international safety requirements of operations mounted ultrasonic level sensor in the filter blood dropper after the plasma filter and added yet another capacitive sensor, which responds to the emergence of air inclusions directly in the blood return line (Patent RF № 2203099 from 27.04.2003). The control panel in the machine consists of a two-line alphanumeric scoreboard indicator, which shows the main parameters of the device, reports of its condition and emergency situations that may arise during the operation.

**Advantages of plasmapheresis with apparatus "Hemofeniks."** Described techniques work with this apparatus is in our opinion the most preferred. It can be successfully used in the practice of critical care, and treatment planning of patients with chronic diseases. It may equally be applied in pediatric practice. Have a number of advantages in terms of urgent as portable and easily transportable (in a special case) unit can be deployed in any more or less suitable areas, including in the system ambulances and disaster medicine. An important advantage is the single-needle type of connection to the patient. This is particularly valuable when the "bad" veins, venous access deficit with extensive burns, etc.

The advantage is the adaptability of the device to the conditions of the suck and venous return. Device practically chooses the most appropriate for the specific conditions of perfusion parameters – duration and the intake and return of blood consistent with a predetermined range of the maximum pressure in the chambers of the blood plasma filter. After establishing the optimal dose of anticoagulant additives and, if necessary, an isotonic sodium chloride solution to the blood flow, the device may further operate virtually automatically.

Only occasionally monitored duration of the phases, mainly expulsion phase, and also conducted periodically replenishing removed plasma volume plasma substitutes, ie, in the process does not require too intense and continuous monitoring and any tedious manipulations. Therefore, a well operator can simultaneously hold at least two or three operations in one place.

With the help of the device "Hemofeniks" can be carried out at the obtaining plasma donors also, especially in these conditions, single-needle connection is
preferred. Getting the required amount of plasma produced quickly enough, and the quality of the resulting plasma meets all requirements of the blood service.

Mobility unit produces autoplasm under surgical departments or directly in the course of operations, as well as in intensive care from relatives. With the help of the device "Hemofeniks" can successfully carry out one-step and continuous plasmaphoresis and even ordinary hemosorption, ie this machine for all its simplicity and miniaturization, can replace a whole range of sophisticated equipment to ensure all tasks efferent therapy and detoxification. It successfully allows hemosorption plasmapheresis or in patients who are in critical condition, even in an unstable hemodynamic and threatening bleeding.

Simple and safe method of membrane plasmapheresis apparatus "Hemofeniks" offer opportunities wider adoption of efferent therapy from outpatient practices to disaster medicine [Popov A.S. et al., 2007].

Conclusion

Material presented in this paper does not claim to be comprehensive analysis of the experience of efferent therapy in a wide variety of acute illnesses, only reveal their role in the pathogenesis of the internal environment with the accumulation of pathological products such as exo- and endogenous origin. Coming cascade of metabolic disorders leading to secondary violations of cellular and humoral immunity to the development of a series of vicious circles that break neither the body nor drug therapy can not. It is these disorders and determines the extent and manifestations of the general outcome of such diseases.

The objective of this work was to study the indications for use of efferent methods of detoxification and correction of the internal environment in the complex of therapeutic measures, accurate selection of the most optimal strategy based on pathogenetic features of the occurrence and course of certain types of diseases and critical states. Among the methods of efferent therapy the most versatile and efficient is plasmapheresis and membrane plasmapheresis using plasma filters "Rosa" seems the most simple, safe and affordable for use not only in large referral centers, but also in virtually any hospital [Voinov V.A., 2012].

Nevertheless, in spite of the simplicity of this method for its development requires special training of medical staff, both doctors and nurses procedural. In addition, they must be well and all other methods of detoxification and efferent therapy – methods
hemosorption, plasma adsorption, ultraviolet blood irradiation and laser beams, electrochemical oxidation and ozonation of blood and extracorporeal membrane oxygenation of blood.

The mobile nature of the equipment and techniques simplicity allows membrane plasmapheresis and pre-hospital emergency care to victims of earthquakes, man-made disasters and other types of mass lesions within the Disaster Medicine [Popov A.S. et al., 2007].

Wider adoption of methods of efferent therapy in clinical practice will undoubtedly increase the quality of preventive and curative care.

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INFORMATION

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