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Respiratory distress syndrome

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There are considered endotoxicosis as the main causes and mechanisms of respiratory distress syndrome development and ground of necessity extracorporeal detoxication for it treatment. There are shown advantages of membrane plasmapheresis.

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

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PREFACE

Acute respiratory damages of lung parenchyma are frequent and serious complications in a number of diseases. The reason for writing this book became an increasing conviction that the main causes of such serious pulmonary disease 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 such 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 can not 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 such acute disease.

LEGEND

ALV – artificial lung ventilation.
BAS – biologically active substances.
CPV – circulating plasma volume.
DIC – disseminated intravascular coagulation
ECMO – extracorporal membrane oxygenation.
ELF – extravascular lung fluid.
PEEP – positive end expiratory pressure.
RDS – respiratory distress syndrome.

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

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 progressing 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 occured 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 a thickening 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 endotoxia – 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 (leaking) 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 [V.A. Voinov, 1992].

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 manifesting signs of respiratory failure and X-ray 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 myocardiopathy 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 [I.A. Eryuhin, B.V. Shashkov, 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, crush 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).

### Tabl 1. Surfactant activity after addition of blood of healthy dogs, healthy people and patients with RDS

<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 gase 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 determed 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) [O.P. Shestenko 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 expiration (PEEP).

One must admit that maintaining pressure of 5-10 cm H₂O 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 ELF volume 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 inoculation 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 FiO₂ 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].

This is understandable since researches described above show that surfactant deteriorates due to infiltration into alveoli of toxic products. That is why, no matter how much surfactant is introduced into the lungs, without exterminating toxic products from
the blood, the newly introduced surfactant will deteriorate as fast and effectively as its own.

These facts made foreign scientists back in the 1970s to resort to using extracorporeal gas exchange using membrane oxygenators, which by that time were made to improve the results of open heart surgery. In animal experiments, it was possible to secure and maintain gas exchange up to three weeks with the help of membrane oxygenators. This enabled them to use the auxiliary extracorporeal membrane oxygenation (ECMO) for acute parenchymal respiratory failure.

The first results of the treatment of RDS with ECMO in some clinics were quite encouraging. Indeed, immediately after connecting a membrane oxygenator gas exchange recovered, the condition of patients stabilized. However, the inverse dynamics of pathological changes in the lung in appreciable extent were not observed. After the procedure there were cases of newly progressed inflammatory and destructive processes. They managed to achieve a successful outcome in only 20-30%, more often in children. In recent years, the effectiveness of ECMO 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].

G.J. Peek et al. (1997) summed up the seven-year application of ECMO in 50 patients with RDS with overall survival of 66%. With transdermal catheterization they were able to achieve speeds of veno-venous perfusion of up to 120 ml / (kg • min) and to provide extracorporeal gas exchange within 207 hours in average. During this period, the patient was required to transfuse up to 19 doses of blood, significant amounts of donor plasma, platelet concentrates, to provide parenteral nutrition clock monitoring and maintenance of highly qualified professionals, which required substantial financial costs much higher than $ 100,000. The use of ECMO for the treatment of neonatal respiratory disorders also required at least $ 50,000 [Roberts TE, 1998]. Given these difficulties and the complexity of the operations of ECMO in themselves, they not widely available. However, extracorporeal membrane oxygenation took place among certain treatments RDS recommended by the said Conciliation Commission.

In some cases, the method of extracorporeal removal of CO₂ and with the help of membrane oxygenators is used but own lungs are supported in a state of functional rest while ensuring constant and almost no oscillating flow of oxygen to maintain an adequate level of oxygenation [Morris A. et al., 1994; Falke K.J., 1997].

In recent years, attempts have been described to use a full or partial liquid ventilation with perfluorocarbons against the maintenance of normal operation of the
gas ventilation or ECMO, which showed quite promising results in the treatment of RDS, both adults and infants [Cox PN et al., 1997; Kolla S. et al., 1997; Yoxall C.W. et al., 1997; Davies M.W., Fraser J.F., 2004]. The use of high-frequency respiratory support against the partial liquid ventilation of the lungs showed no advantages over conventional volumetric ventilation [Smith K.M. et al., 1997].

Nevertheless, conventional methods of intensive therapy with various ventilation are mostly used still [Avdeev S.N., 2005]. S. Vasilyev et al. (1995) summarized the experience of the 25 centers in the U.S. and Europe, where there were 1,426 patients with RDS. All had mechanical ventilation. If by the beginning of ventilation with FiO₂ 0.5 and not more than hypoxemia, hypercapnia, or were not observed, the survival rate was 63.6%, if with such a background, there was a significant hypoxemia and hypercapnia present, then 33.3% of the patients survived. If only acute respiratory failure was observed, the surviving 40% of patients, with multiple organ failure survivors were not more than 10%.

One can find information about the financial cost to the conservative treatment of RDS [Angus DC et al., 1996]. Average SMS cost was $ 79.355 (for survivors - $ 83.437, for the dead - $ 71.073), which is not much less than with ECMO. Given that in the U.S. annually RDS develops in 126000 - 159000 patients (mortality rate - 30-60%), the total cost of treatment ranged from 9.6 to 12.7 billion dollars. At the same time, a therapy that would reduce the cost of treatment by at least 1% would result in a total savings of up to $ 100 million a year.

The present analysis shows the complexity of the problems in the treatment of RDS, but at the same time and almost no pathogenetic approach to its therapy, which consists in ignoring facts endotoxic nature of lung and other organs lesions, and as a result - do not use the methods of detoxification, besides a number of cases of hemofiltration against the ECMO.

In the 70-s membrane oxygenators of foreign origin were not available to us, and the Russian ones did not exist. Therefore, the Research Institute of Pulmonology of the USSR (G.A.Rusanov, E.N.Danilov, V.A.Voinov) in collaboration with the association "North" (L.L.Plotkin, B.M.Zelikson, B.Ya.Basin) since 1974 was working on the development of methods of extracorporeal membrane oxygenation, and in 1979 was created the first domestic membrane oxygenator "North". After a series of experiments on animals, it was admitted into clinical practice and was originally used with a heart-lung machine during open heart surgery [Voinov V.A., 1985].
However, our own initial attempts to use of extracorporeal membrane oxygenation in RDS did not give the expected results due to the inability to stop the progression of pathological processes in lungs and multiple organ failure, despite the correction of impaired gas exchange during operation.

These failures on one hand, and the results of experimental studies showing the toxic nature of lung lesions and other organs, on the other hand, convinced us to use methods of detoxification. In these conditions, only direct blood detoxification methods can stop the progression of the process, break many vicious circles.

Methods of detoxification in respiratory distress syndrome

From 1980 to 1990 the most affordable and safe method of detoxification for RDS was hemosorption (hemocarboxyperfusion) using activated carbon grades SKN, SUGS, FAS, VNITU etc. When passing through the column up to 3-4 CBV there was fairly complete elimination of many pathological products and even delay and fixation of live bacteria that, for example, when an infection caused by Pseudomonas aeruginosa, hemosorption was the only truly effective treatment due to inadequate antibiotic therapy. Decreased were the levels of middle molecules, blood toxicity in general (according protozoa survival time), with improved overall condition, changes in visible in X-ray lungs were subjected to regression [Voinov V.A. et al., 1985, 1989, 1992].

Hemosorption proved effective with destructive processes and even pulmonary gangrene. Naturally subjected to ichorization parts of the lungs are not able to recover their structure but then there was decline in perifocal changes, intoxication, allowing patients to prepare more quickly for the inevitable surgery, which was easier to bear. What was surprising is the disappearance of a completely unbearable smell from the mouth while breathing in spite of the remaining portions of gangrene. This indicated that the odor is formed not only in the respiratory tract, but mainly by penetration of pathological blood products through the air-blood barrier. I mean, that was the smell of the blood itself, it reflected the accumulation of vast amounts of pathological waste products.

However, in advanced stages of RDS against severe parenchymal respiratory failure that required mechanical ventilation, hemosorption was no longer able to change the course of the pathological process. The level of middle molecules, instead of the expected decline, increased above the initial, apparently due to leaching of the depot and damaged tissues with heparinization and the improvement of microcirculation and
blood rheology. The clinical picture also showed an increase in the severity of multiple organ failure.

In these conditions, only **extracorporeal membrane oxygenation** (ECMO) at a rate of 25-30% of the cardiac output and blood flow of up to two days made it possible to gain time, that is, to support the exchange of gases at the minimum adequate level and during this time to ensure a more active detoxification. Only the combination of a massive detoxification (hemosorption to three sessions during the day) due to ECMO made it possible to provide a regression of organ damage at very advanced stages of RDS. Out of ten completely hopeless patients seven were rescued [Voinov V.A., 1985, 1995].

It should be noted that, according to GJ Peek et al. (1997), for the treatment of RDS with ECMO it took an average of 207 hours and a lot of blood, plasma, platelet suspension and other drugs, which explains the extremely high cost of such courses (over 100 thousand dollars). In our cases, it took for the relief of the same RDS extremely severe for only 20-40 hours. And the difference in treatment strategy was only in one aspect — we held with ECMO an intense detoxification using hemosorption, which is still ignored in US and Western Europe.

Analysis of the treatment of 153 patients with RDS who were treated in the period 1998-2003 was conducted, and 67 patients were treated with traditional methods of medical treatment, and 86 patients, comparable in severity of RDS, the detoxification using hemosorption, plasmapheresis, photohemotherapy and indirect electrochemical oxidation of blood was conducted.

Hemosorption was carried out with 1-2 passing blood volume through columns SKN, SUGS, FAS or VNIITU-1. Membrane plasmapheresis was performed using plasma filters PFM-800 or PFM-01-TT «Rosa» on devices «Hemos-PF» and AMP-TT «Hemofenix» in the mode of plasma exchange to remove the 1.2-2.5 liter or 0.5-1.0 volume of circulating plasma (CPV), and the replacement of fresh frozen plasma donation. UV of blood was conducted using the "Isolda" machine and laser irradiation of blood in vitro - apparatus "SHUTTLE". Indirect electrochemical oxidation of blood was conducted - EDO-4. With extremely severe RDS what was used is extracorporeal membrane oxygenation (ECMO) using oxygenators "North" or "MOST" with venovenous perfusion at a rate of 1.0-1.5 l / min lasting 15 to 44 hours, with hemosorption every 6-10 hours.
All patients received medication and traditional therapy, and with the development respiratory failure - mechanical ventilation (ALV), in severe cases, with a positive end-expiratory pressure (PEEP).

There are 3 allocated degrees of 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 on 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>Severity criteria</th>
<th>Respiration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Middle molecule level</td>
<td>PaO₂</td>
<td>Area of lung shading in X-Ray</td>
</tr>
<tr>
<td>I</td>
<td>Moderate</td>
<td>350.0±22.5</td>
<td>68.2±1.8 (at FiO₂ 0.4)</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>
</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>
</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>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>ИТОГО</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 detoxicating 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>
<th>Detoxification (hemosorption, plasmapheresis)</th>
<th>Detoxification + ECMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only traditional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>73.33%</td>
<td>31.03%</td>
<td>30%</td>
</tr>
<tr>
<td>Highly severe</td>
<td></td>
<td></td>
<td></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 RH 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].

Endotoxemia, which determines the severity of RDS and the scale of destruction of lung parenchyma, is quite multicomponent. It consists of bacterial endo- and exotoxins, mediators of inflammation and tissue destruction, and proteolysis products as well as lipid peroxidation. All of these toxins disrupt cell membrane permeability, including vascular endothelial with access not only to interstitial fluid, but also to the protein. Such a toxic edema underlies the development of RDS, but to the same extent it affects other organs and systems, leading to multiple organ failure [Voinov V.A., 2007].

However, only detoxification, achievable through hemosorptions is not enough for full therapeutic effect, because the body is still in a state of immunosuppression due to which at one time opportunity to develop this serious complication was created. More stable result is achieved through conduct of plasmapheresis with replacement of remote plasma of the patient with "incompetent" antibodies, immunoglobulins, complement, opsonized 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. At the same time, in fairness, it should be emphasized that 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 extrasystoles were detected.

Donor plasma was not available, so the first phase of efferent therapy aimed at detoxification included hemosorption of 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 parts 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 fresh frozen plasma to the donor, 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.

It should be emphasized that this patient was in one of the district hospitals of Leningrad region and detoxification on the road has been possible with the help of a portable domestic unit AMP-TT "Hemofenix", with which you can conduct both hemosorption and plasmapheresis.

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; 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.

This also applies to cases of RDS of premature infants, where there is indeed a deficiency of surfactant, but the most common case is development of RDS "adult" type - a toxic pulmonary edema as a result of infiltration into bloodstream of the fetus of endotoxins of the mother in cases of violation of pregnancy, which causes premature birth. Therefore, for such a newborn the use of detoxification is more justified - specifically developed method of syringe membrane plasmapheresis [Voinov V.A., 1996], after which there is no need for additional introducing exogenous surfactant.

The following clinical observation may serve as an example.

Child M. with body mass of 700 gr was born at the time of 22 weeks with severe pre-eclampsia in a critical condition. Apgar index was 4-6. On the second day after birth we observed remaining severe hypoxia, not interrupted by mechanical ventilation of lungs. X-ray reveals practically total shading of lungs in the degree of density equal to the shadow of heart and liver. Anuria. On the screen we can see only ECG complexes with a straight line of registration of microcirculation from the sensor on the finger. Started syringe membrane plasmapheresis with the help of plasma filter “Rosa”. After
replacing 50% of CPV on the screen we can already see oscillations with a finger oximeter - start of recovery of hemodynamics and microcirculation. At the end of plasma exchange (1.5 CPV) diuresis appeared. The next day, the state stabilized and in about half of the lung X-ray fields were already aerial. In the future, there have been observed quite a fast recovery dynamics of the lungs, kidneys, liver and recovery of the child.

As noted above, adult respiratory distress syndrome is never isolated. It is often accompanied by a lesion in varying degrees, of other vital organs and, above all, kidney [Bolton WK, 2010]. Acute renal failure (ARF) is observed in one third of patients with acute pneumonia [Murugan R. et al., 2009]. It has long been observed that even in itself artificial lung 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].

Often, ARF develops in the presence of sepsis or sepsis joins an already developed kidney disease [Schrier RW, Wang W., 2004; Bouglé A., Duranteau J., 2011; Mehta RL et al., 2011]. Risk factors include severe burns, pancreatitis and peritonitis traumatic shock syndrome and prolonged compression, eclampsia [Kirkovski VV, 1997; Mosier MJ et al., 2010; Serov VN et al, 2011]. Mortality is as high as 70-80% [Ko G.L. et al., 2009; Chou Y.H. et al., 2011].

However, as with RDS, with a variety of etiologic factors in the pathogenesis of ARF lies toxic damage of the renal parenchyma. Violations of the permeability of the 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 of the working group on ARF (ADQI), the criteria for inclusion of patients “at risk” is decreased urine output to less than 0.5 mL / kg in 6 hours, to a group of "kidney disease" - less than 0.5 mL / kg 12 hours, the group "renal failure" - less than 0.3 mL / kg over 24 hours or anuria for 12 hours [Bellomo R. et al., 2004]. The risk of death in a group of "at risk" - 13%, in the "disease" - 40%, and "failure" - 80% [Stainvall I. et al., 2008].

Such unfavorable prognosis in cases of ARF, of course, requires intensive care. However, as with RDS, when trying to treat respiratory failure through various methods of artificial ventilation, in cases of acute renal failure of excretory function some tend corrected it through the measures of removing the accumulating fluid by hemodialysis or various methods of 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 was explained by the desire to eliminate the only visible disorders - breathing with RDS diuresis in case of ARF. That is, it was actually symptomatic therapy not affecting the essence of pathology - endotoxemia, which is the basis of these organ disorders. And really - the mortality in these patients remained quite high - up to 50-70%, regardless of the choice of methods of "renal replacement therapy" - dialysis, intermittent or continuous veno-venous hemofiltration [House A.A., Ronco C., 2008; Russel J.A., 2008; Palevsky P.M. et al., 2009; Захаров М.В., 2010].

But the survivors in the long term often showed signs of chronic renal failure [Lo LJ et al., 2009; Hsu C.Y. et al., 2009; Chawla L.S., 2011]. In spite of the applied methods of renal replacement therapy (continuous or intermittent hemofiltration), after discharge from hospitals in mortality during the first year was 23% and in the second year of another 7.6%, which in the end was 65.7% [Van Berendoncks AM et al., 2010]. Using only hemofiltration we cannot remove macromolecular and no less toxic products, including fibrinogen, which causes the need to use 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 - a major factor tanatogenesis.

In particular, at high removal of cytokines such as TNF-α IL-1β, other cytokines - IL-6 and IL-8, more unfavorable in prognosis, were delayed in the body [Gromova E.G. et al., 2002]. A.M.Karas’kov et al. (2002) also noted that using hemodiafiltration can reduce the levels of TNF-α, IFN-γ and IL-4 with the correction of the flow of critical states, however, such a procedure did not influence the course of infection. That gave in correction only with plasmapheresis that contributed to the restoration of decreased production of INF-γ improvement of cellular and humoral immunity. Schmidt J. et al. (2000) used a combination of plasmapheresis with continuous hemofiltration.

For a more complete restoration of immune mechanisms appropriate combination of hemosorption and plasma exchange with methods of photohemotherapy. Oxidative methods have also been successful, mainly indirect electrochemical oxidation, meaning addition to the infusion solution of 200-400 mL of 0.06% of sodium hypochlorite.

Described in more detail is an example that reveals the pathogenesis of RDS and rationale for the use of methods of efferent therapy in case of development of this complication, and reflects a number of other clinical situations arising in severe burns and trauma, acute inflammatory diseases of the abdominal cavity, etc. In all these cases efferent therapy, however, cannot provide stable effect without toxicity source elimination, usually by surgical methods. But sometimes without prior detoxification it is
impossible to provide a secure environment for operative treatment, and after surgery efferent therapy promotes more rapid normalization of homeostasis, a more complete and permanent cure [Chanchiev Z.M., 2012].

One can often hear concerns that during plasmapheresis important antibodies are extracted that developed after vaccination (smallpox, measles, tuberculosis, etc.). In a special study U.Schöntrmarck et al. (2011) actually showed a decline in measles, however, in an average of 64 days after a course of plasmapheresis they were fully restored to their original level.

It seems more reasonable, an active detoxification – hemosorption or plasmapheresis. And, indeed, almost always after removing “toxic press” from kidneys restoration of their excretory function happened. The next day the urine output was no less than 500-700 ml. In parallel, improved was functional status of other vital organs - lungs, liver, heart, brain [Voinov V.A. et al., 1995, 2012]. Especially revealing was the treatment of a patient with RDS and full anuria with eclampsia, which lasted for a month after delivery. After the session of hemosorption, the next day diuresis was already 500 ml, and after repeated sessions it recovered fully followed by a rapid recovery of the patient.

Besides kidneys failure occurs in other vital organs to some degree. Upon accession of acute liver failure there is an increase of bilirubin levels much, and, even more, of enzymes - ALT and AST. And removing the "toxic press" from hepatocytes rapidly normalizes liver function. At the extreme hypoxia there is impact on structures of the brain, down to the deep hypoxic coma. Growing frustration at both the central and peripheral circulation is present.

Furthermore, toxic products circulating in the blood, not only damage the vessel walls, but also the cells of the blood itself. The first is excited platelet aggregation with the formation of platelet microaggregates, which is the first step in the development of DIC with all its consequences. The risk of bleeding rises, and not only from the lungs in the form of hemoptysis, but, even more dangerous, from profuse bleeding from erosions and acute ulcers of the stomach. Their appearance can also be associated with endotoxicosis and disorders of microcirculation at the level of the mucous membrane of the stomach. In places where there is tissue ischemia soon appear the sources of their destruction with the appearance of erosions and acute ulcers, of which at any time may cause bleeding.

Given the extremely severe cases of RDS along with multiple organ failure and hemodynamic disturbances occur, making it difficult to carry out any procedures
extracorporeal detoxification. However, domestic device «Hemofenix» provide the possibility of plasmapheresis with plasma filter «Rosa» and hemosorption with any available hemosorbert, even with unstable hemodynamics, supported by a relatively satisfactory level only with sympathomimetics. This was possible when taking into account the small volume of prefilled extracorporeal circuit of this unit, not to exceed 65-70 ml, which makes it possible to provide treatment even for children up to the age of breast.

Therefore, treatment of patients with RDS in critical condition is a rather difficult task. Recently, we had developed a treatment strategy taking into account all sides of the pathogenesis of RDS and acceding multiple organ failure.

Given the large proportion of the probability of the circulation in the blood of a number of pathogens at the first stage it is advisable to resort to massive hemosorption, which in addition to a significant detoxification by passing through a molecular 1-2 bcc column provides and decontamination - a delay on the sorbent agents, both living and dead, which leads to stabilization of the patients. Functions not only light, but all other vital organs are improved.

In the second stage, the very next day, you can start plasmapheresis to remove at least 60-80% of CPV and substituting it with an equal volume of fresh frozen plasma donation. Thus, in addition to detoxification we have correction ("prosthesis") of the immune system with a reduction of not only humoral but also cellular immunity. Very often these sessions of hemosorption and plasmapheresis may be enough for the body itself to restoreits autoregulation and end the critical state.

It should be taken into account that high risk of bleeding requires special tactics and use of anticoagulants. First of all, heparin is completely excluded , and the prevention of blood thrombosis in the extracorporeal circuit is provided by a solution of sodium citrate. The best of them is domestic solution "CPG" (citrate-phosphate-glucose), which is more efficient than imported solution ACD-A. In the first active principle - sodium citrate - concentration of 3.2%, and ACD-A is only 2.2% under similar other constituents.

The following observation serves as an example of a highly difficult treatment of RDS in development.

*Girl D.*, 2.5 years old, weighing 15 kg, suffered from acute lymphoid leukemia. After high-dose chemotherapy with stem cell transplantation severe RDS 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 RDS 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 RDS when the negative dynamics of its development already emerges. Thus, it is necessary to take into account increase the severity of RDS, fairly rapid in some cases, where just a few hours you can "lose" these patients.
Daria, 2.5 years old (15 kg). Diagnosis - lymphoid leukosis. After high-dose chemotherapy and stem cell transplant respiratory distress syndrome, multiple organ failure and sepsis in the background complete lack of white blood cells developed. First hemocarboperfusion was performed, then plasma exchange with the «Hemofenix» device. Improvement, urine output recovered, the temperature returned to normal. However, because of leukopenia in 2 weeks new impairment, sepsis and hemocarboperfusion escalated again and plasma exchange has been completed, after which the recovery was evident.
The same girl a week after her final plasma exchange session.
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INFORMATION

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In efferent therapy division of Pulmonology clinic at the faculty of post-graduate education of St. Petersburg First State Medical University of I. P. Pavlov a course of thematic augmentation is held: "Efferent therapy in intensive care and internal medicine" (144 hours) with the issuance of the relevant certificate and certification cycle for Nurses "Nursing in efferent therapy."

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