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Immunological Pathogenesis of Septic Reactions and Elimination of Triggers and Mediators of Inflammation

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1. Introduction

Modern intensive therapy is armed with very sophisticated methods, however sepsis is still one of the most challenging issues of medicine. Death rate in patients caused by sepsis remains high and reaches about 30-80% (Yegenaga I. et al., 2004). This problem is especially important in oncology, as every sixth septic patient has a diagnosis of cancer; and the death risk of such patients is 30% higher (Angus D.C. et al., 2001).

The established bacteriologic paradigm of sepsis implies an infectious component for its development. The priority in the pathogenesis of this disease has been assigned to microorganisms, and therefore sepsis is regarded primarily as an infective disease. However, over the last decades there have appeared tendencies for an essential revision in the understanding of mechanisms of sepsis development; inflammatory reactions of the organism are now regarded as important as infection. In particular, according to a current definition, approved by American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference, "sepsis is a systemic inflammatory response syndrome developing in response to an invasion of different pathogenic microorganisms, which is diagnosed if an infective agent and two or more signs of the systemic inflammatory response are present" (USA, Chicago, 1991).

Systemic inflammatory response syndrome (SIRS) includes the whole set of the clinical manifestations of systemic inflammatory response (SIR), which is a generalized form of inflammatory reaction and is formed as a result of an excessive immune cell activation that produce different types of mediators (cytokines, leukotrienes, thromboxanes, etc.). SIRS is a necessary component of sepsis, however, it is not the same, as SIRS may be induced by different non-infective causes such as trauma, pancreatitis, etc. Thus, signs of systemic infection are necessary to prove diagnosed sepsis. Besides, it should be taken into account that bacteremia is not pathognomonic to sepsis. The rate of diagnosed bacteremia even in the most serious cases does not exceed 45% if accurate techniques of blood sampling and modern microbiologic methods are applied. Detection of microorganisms in the patient's peripheral blood with no clinical and laboratory test conclusion of SIRS may be considered as transitory bacteremia that is not necessarily caused by septic process. Some authors

recommend differentiating localized focus of infection from true sepsis even if it is associated with the symptoms of systemic inflammatory reaction. In about half of cases (30-60%) when clinical symptoms of sepsis were evident, it was impossible to isolate live microorganisms from the blood or find the focus of infection.

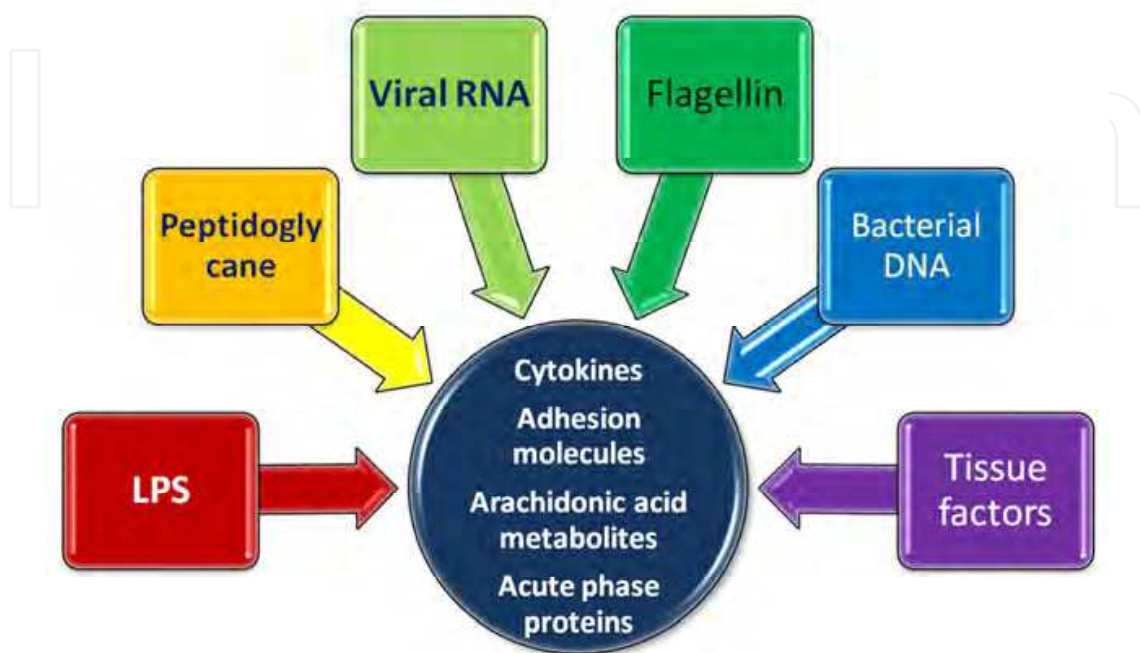


Fig. 1. Triggering factors and mediators of sepsis.

The disease status that demonstrates the whole set of septic symptoms but lack of infection is regarded like pseudosepsis or sepsis-like syndrome. Trigger factors initiating systemic inflammatory response might be derivatives of microorganisms (exo- or endotoxins) rather than microorganisms themselves, or even factors of non-infective origin including endogenous factors (such as tissue factors, elastin, thrombin, etc.), which appear primarily during organ or tissue damage (Fig. 1) as a result of traumas, burns, etc.

Clinical symptoms of sepsis as well as organ or multi-organ dysfunction syndrome (MODS) may develop in response to endo- and exotoxins of microorganisms in the absence of bacteremia (septicemia) or localized focus of infection. The macroorganism reaction to bacterial products displays totally the whole symptom complex that is characteristic for bacterial sepsis. LPS poisoning does not only induce clinical presentations of sepsis and septic (endotoxic shock), but leads to pathomorphologic changes characteristic for septic conditions (Angus D.C. et al., 2001).

Present understanding of sepsis states that it is a systemic inflammatory response of the macroorganism, which develops as a result of interaction of the immune system with bacteria or their toxins and is mediated by the over-expression of a complex of humoral factors: cytokines and other substances (platelet activation factor, metabolites of arachidonic acid, endothelin-1, and complement components). Local tissue damage during SIRS arises from the release of active oxygen forms, proteases and escalation of cytokine synthesis. Such vision of sepsis pathogenesis suggests that new diagnostic and prognostic markers of this condition should be identified in patient's immunologic parameters. Following this

concept, new therapeutic strategies of inactivation or elimination of SIR triggers and mediators are being developed.

2. Bacterial toxins: triggers of inflammation

Infective agents have various factors of virulence which can affect protective reactions of the body. In septic and inflammatory conditions cascade of events initiated by microbes and their products may develop out of control. Immune effectors recognize pathogens, firstly, by innate immunity receptors detecting different pathogen-associated molecular patterns that include various components of microbial cell wall (such as, LPS -lipopolysaccharide, peptidoglycan, lipoteichoic acid, mannan, flagellin, bacterial DNA, viral double-helical RNA, glucan and intracellular components, etc.)

Bacterial toxins, primarily LPS of gram-negative bacteria, have significant impact on activating mechanisms of inflammation and may induce or potentiate systemic inflammatory response in the absence of microbial cells. In particular, it was shown that in humans LPS in the minimal dose (4 ng/kg) initiates release of inflammatory mediators, alterations of hemostasis and fall of the blood pressure resulting from the decrease of the cardiac output and vascular resistance. Sepsis-like conditions were described in volunteers after injections of high endotoxin doses as well as in patients receiving therapies based on LPS-immunomodulators (Laurenzi L. et al., 2004, Zucker T. et al., 2004). Sepsis-like syndrome is observed in patients after cardiac surgery, closed injury, and in patients resuscitated after cardiac arrest.

One of the major mechanisms of infection is penetration of normal microflora and substances including endotoxins into blood circulation from the natural organism biocoenoses, mainly from the bowels (Annane D. et al., 2005). Translocation of bacteria and their toxins into the bloodstream might be caused by changes in the mucous intestine tunic (Moore F.A. , 1999). Nevertheless, impairment of the intestine permeability most often has a secondary origin and results from the SIR to trauma, surgical stress, burn, high-dose antibiotic therapy and other damaging factors (Deitch E.A.&Bridges R.M. , 1987, Balzan S.et al., 2007). In cancer patients, risk of bacterial toxin translocation increases due to disorders of the intestine mucous barrier function caused by the major disease and especially, by anti-tumor aggressive therapy. An additional unfavorable factor is older age of patients because of the age-related changes in the intestines permeability. These patients, despite of the widely accepted view about immunity involution and down-regulation of immune reactions in the elderly, demonstrate an enhanced response to bacterial toxins. For example, patients over 65 have a more significant drop of the blood pressure after injections of minimal LPS doses (2 ng/kg) compared with younger individuals. The phenomenon is apparently linked to the systemic chronic inflammatory reaction of the elderly, associated with a higher initial level of pro-inflammatory factors.

When LPS enters blood circulation, it partly links to the LPS-binding protein (LBP) and the newly formed complex interacts with CD14-positive cells, such as macrophages. LPB potentiates LPS transport to receptors of macrophages (CD14) and stimulates functional activity of these innate immunity effectors (Takeshita S. et al., 2002). The endotoxin-shipping function in the blood also refers to the soluble circulating macrophage CD14-receptors. A number of studies showed an increase in these markers in patients with sepsis, including cancer patients (Myc A. et al., 1997, Nijhuis C. S. et al., 2003).

Our data show that LPS serum concentration increases in patients with sepsis aggravated by organ failure or MODS. Particularly, in contrast to healthy volunteers, whose blood almost lacks LPS, patients with kidney or hepatic failure with no symptoms of SIRS showed moderate increase of LPS serum concentrations (0,1-0,2 IU/ml), while patients with sepsis and septic shock had markedly increased blood serum concentrations of this bacterial toxin - median parameter in the group was 0,55 IU/ml, sometimes reaching 6,25 IU/ml (Fig. 2).

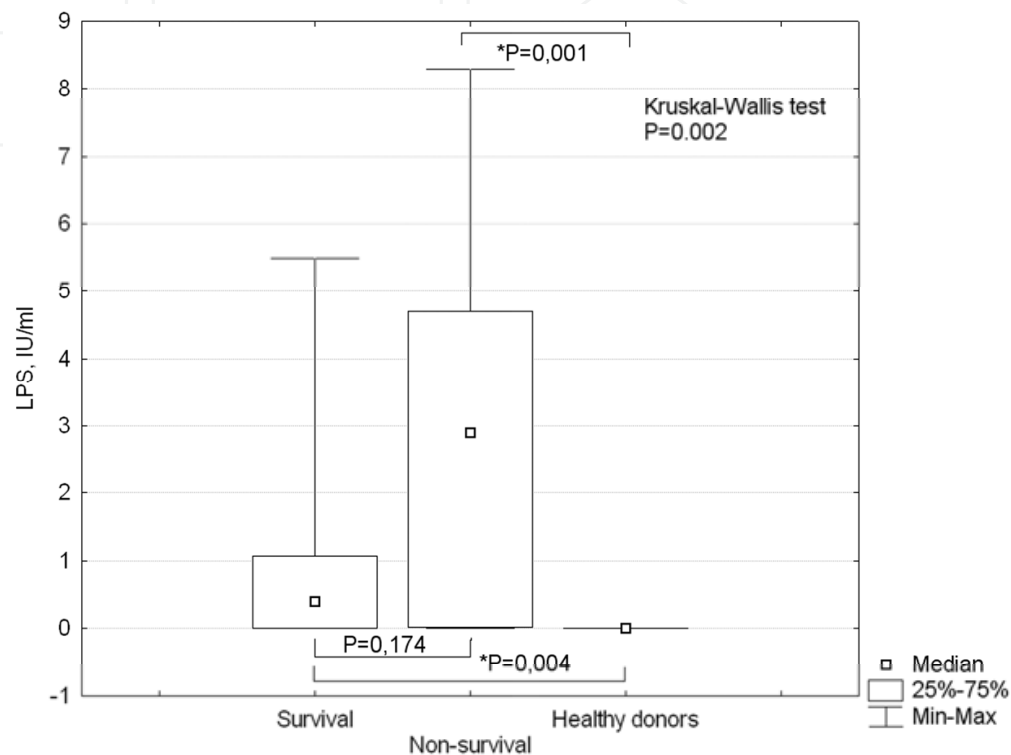


Fig. 2. Comparative analysis of LPS serum level in groups of survival and died patients with sepsis and in healthy volunteers.

A high LPS concentration in peripheral blood is generally associated with a drop of LPB level. In patients with sepsis the ratio of blood serum concentrations LPS/LPB is on average ten-fold higher than in healthy individuals. Therefore, dynamic growth of LPS concentration and decrease of LPB level in sepsis may be considered as negative prognostic factors.

3. Cytokines

Over the last years, a lot of data have been accumulated that discuss the role of endogenic bioregulators of different origin (cytokines, kinins, phospholipids, arachidonic acid metabolites, etc.) in development of structural and functional alterations leading to systemic inflammatory reactions and sepsis. Immune mediators - cytokines have an absolutely important role in inflammation pathogenesis. Their high biologic activity and a small difference between effective and toxic concentrations make them key factors both in natural physiologic processes and pathologic conditions. As it was mentioned earlier, a triggering mechanism of SIRS, besides bacteria and/or their toxins, might be a trauma, including surgical intervention. With no microbial components it may also initiate an inflammatory cascade, leading to cellular damage and organ dysfunctions. Different endogenous factors,

so-called alarmins, which are activated by tissue damage (for example, necrotic cells, RNA, urine acid crystals, etc.), may bind leucocyte receptors and induce systemic inflammatory response or "sepsis with no infective agent". A term "alarmin" was suggested by J. Oppenheim for endogenous stress molecules that provide signals about tissue and cell damage (Oppenheim J.J. & Yang D., 2005).

Thus, excessive concentrations of these endogenous modulators provoke development of pathophysiologic abnormalities leading to organ failure or MODS. However, despite numerous studies looking at prognostic or diagnostic significance of cytokine concentrations in the serum of patients with purulent and septic complications, there is still disagreement on the topic. Serum cytokine low levels are registered in the peripheral blood of many patients regardless clinical symptoms of sepsis or septic shock. At the same time, some authors report data of increased concentrations of several cytokines such as interleukin(IL)-8, tumor necrosis factor (TNF) α , IL-6 in the peripheral blood of patients with sepsis (Calandra T. et al., 1990, Anderson R. & Schmidt R., 2010, Găini S. et al., 2006).

Risk of SIRS development is extremely high in cancer patients, as the necessary extensive surgery stimulates release of pro-inflammatory cytokines that may promote development of systemic inflammatory response (Hildebrand F. et al., 2005, Lenz A. et al., 2007). Some authors suggested diagnostic and prognostic significance of TNF α serum level (Calandra T., 1990). The results showed both increased as well as similar to the control group concentrations of TNF α in serum of patients with severe sepsis. An unfavorable course of the septic process was observed in the cases of low basic TNF α level or its negative dynamics (TNF α level dropped from $30,4 \pm 2,7$ pg/ml to $15,8 \pm 6,3$ pg/ml). Originally high TNF α in the blood of septic patients ($1020,7 \pm 30,1$ pg/ml) was considered as a "cytokine cascade out of control". They also presented data demonstrating that intensive therapy in the group of patients with originally high TNF α concentration led to its significant decrease (from $680,4 \pm 32,7$ pg/ml to $450 \pm 16,7$ pg/ml), which was associated with favorable prognosis. TNF α level varied in a wide range from 50 to 3500 pg/ml in patients with septic shock. Median TNF α level was 180 pg/ml in the group of survived patients; and 330 pg/ml in the group of the deceased. On the basis of these data, contradictory conclusions were made about prognostic significance of pro-inflammatory cytokine serum levels in general and TNF α , in particular. However, many researchers agree that both high and low TNF α serum levels in critical conditions may be regarded as a poor prognostic parameter (Martin C. et al., 1994, Quinn J.V. & Slotman G.J., 1999).

According to our data, only the concentration of IL-6 was significantly increased in the peripheral blood of cancer patients with sepsis (Table 1). The highest mediator levels were observed in patients with septic shock. A probable cause of the pro-inflammatory cytokine increase in the patients' blood could be its overproduction by the resident macrophages, in particular, by the hepatic Kupffer cells. Besides TNF α , IL-6 is one of the probable markers of severity of an infective or non-infective stress. It induces production of a wide range of proteins of the acute phase that regulate inflammation process. In septic shock, the cytokine may directly affect organs and tissues; in particular, it may suppress myocardium. Various studies investigated the role of this cytokine in pathogenesis of septic shock, MODS and other systemic processes and its prognostic significance; however, their conclusions are somewhat contradictory (Anderson R. & Schmidt R., 2010, Pinsky M.R., 2004).

Groups	IL-6	IL-8	IL-10	INF γ	TNF α	TNF β	IL-1 β	IL-4	IL-17
Cancer patients with sepsis	203* 61÷494	17 6÷130	48 31÷163	0 0÷16	4 0÷30	4 4÷26	1 0÷28	6 3÷13	31 0÷73
healthy volunteers	0 0÷1	3 0÷11	80 0÷108	2 0÷16	0 0÷0	0 0÷9	0 0÷0	10 2÷12	9 6÷19

* – significant difference compared to the control group of healthy volunteers (P<0.01)

Table 1. Cytokine profile of cancer patients with sepsis compared to healthy volunteers (median, 25th ÷75th quartiles), pg/ml.

On the whole, the above data suggest that determination of free cytokine serum concentrations in the peripheral blood of patients with septic complications presents little information, except for IL-6, which is statistically significantly increased in patients with sepsis, and, especially, with septic shock. Therefore IL-6 is the only serum cytokine, which concentration might be recommended as a marker for sepsis. A possible reason of low importance of the cytokine profile determination in sepsis may be due to the fact that commercially available kits are designed to evaluate concentrations of free (soluble) cytokines only. It is a serious obstacle for the estimation of the total cytokine concentrations secreted into the blood circulation. Even if free cytokines are not detected in the blood, their receptor-bound complexes may be circulating. As a result, “hidden cytokinemia” – high cytokine concentrations non-detectable by conventional methods – may take place.

Therefore, low levels of serum cytokines do not necessarily reflect the true mediator concentrations in blood serum and may result not only from insufficient activity of immune effectors of cancer patients, but also from specific binding with increased concentrations of cytokine soluble receptors. A number of studies reported on the statistically significant increase of concentrations of soluble cytokine receptors: TNF receptors (sTNF-R I and sTNF-R II) (Zhang B.et al., 1998), IL-1 – sIL-1 RII (Müller B., 2002) and decrease of soluble IL-6 receptor (sIL-6 R) (Frieling J.T.M.et al., 1995, Zeni F. et al., 1995) in patients with sepsis. However, other researchers presented different results (Barber M.D.et al, 1999).

The data of our studies showed that only sTNF-RI (p55) serum level was significantly more enhanced in cancer patients with sepsis compared with control group of healthy volunteers. However, the comparative analysis of cytokine and their soluble receptor concentrations in the blood of survived and deceased patients with sepsis showed that simultaneous increase of IL-6, IL-8, IL-10, sTNF-RI, sIL-1RII and sIL-6R was associated with poor prognosis. Probably, the mentioned facts result from the so-called “cytokine storm” and reflect the extreme imbalance of the immune system in sepsis leading to the fatal outcome. This suggestion is supported by the increased level of both pro-inflammatory cytokines (IL-6, IL-8) and anti-inflammatory IL-10 in the patients died from sepsis

Comparative studies of immunocompetent cell potential for cytokine secreting presented more precise data. The level of spontaneous production of these endogenous bioregulators characterizes the original physiologic activity of the blood cells. The intensity of the stimulated cytokine production helps to determine the potential reactivity in response to a possible infection.

The obtained data from our studies showed that blood cells of septic cancer patients with spontaneous overproduction of certain cytokines (IL-6, IL-8) are mostly non-responsive to any stimulation. The observation suggests that immune effectors in this group of patients are over-stimulated.

The inflammatory reaction in response to trauma or infection is induced mainly by innate immunity and develops rapidly at the early stage. Endogenous inflammation mediators synthesized by immune cells in response to microbial components or tissue factors are released within few minutes and may peak within 1-3 hours in peripheral blood. These factors play a major role in the formation of the protective response to infection (they enhance bactericidal activity of phagocytes, promote recruitment of leukocytes to the infection site, stimulate hemopoiesis, and cause fever). However, inflammatory over-reaction leads to an excessive release of inflammatory mediators both of peptide (cytokines) and lipid nature (metabolites of membrane lipids -leukotrienes, thromboxanes, platelet activation factor). These substances, besides protective functions, are highly toxic and may cause hemodynamic imbalance, metabolic and pathologic alterations that are characteristic for sepsis and septic shock. Activation of anti-inflammatory factors, as well as of inhibitors of inflammatory mediators (prostaglandin E₂, IL-1Ra, IL-10 and TGF- β), takes place during SIRS and is considered as compensatory anti-inflammatory syndrome, a protective response limiting tissue damage by endogenous pro-inflammatory factors. On the other hand, prevalence of anti-inflammatory mediators may lead to immune suppression and anergy of immune cells (Keel M.&Trentz O., 2005). Evidently, both hyper- and hypo-inflammatory phases may follow each other or develop independently from each other, according to the original reactivity of the organism. Both conditions of hyper- and hyporeactivity are equally dangerous and may cause fatal outcome.

4. Functional activity of leukocytes

So far a lot of data have been collected to characterize immune status of cancer patients with suppurative septic complications (Martin C., 1994, Quinn J.V.&Slotman G.J., 1999, Anderson R.&Schmidt R., 2010, Pinsky M.R. et al., 2004, Zhang B. et al, 1998, Frieling J.T.M.et al., 1995). Although most of the studies look at parameters of humoral immunity, particularly, at assessment of cytokine profile, a higher interest has been seen in studying functions of immune competent cells over the last years. Special attention is aimed at effectors of innate immunity (natural killers, granulocytes and monocytes), which play a key role in pathogenesis of sepsis (Zeerleder S., 2005). A number of authors show an increasing suppression of cellular immunity with septic background that reveals as decreased function of immune competent cells due to high rate of immunosuppressive agents (IL-10) and decrease of regulatory peptides (IL-12). On the other hand, there are data that prove enhanced production of pro-inflammatory cytokines (IL-8, TNF α , IL-6, IL-1 β) in cancer patients, which level is many times higher than that in healthy individuals (Rigato O.et al., 1996, Kumar A.T. et al., 2009). The logic consequence of this phenomenon may be higher cellular functioning, mostly - innate immunity effector cells function. In the environment of bacteriemia and bacterial toxicity these cells are responsible for natural resistance to infectious agents. However their super activation triggers cascade hyperproduction of inflammatory mediators which initiate SIRS (Angus D.C. et al., 2001, Hildebrand F. et al., 2005).

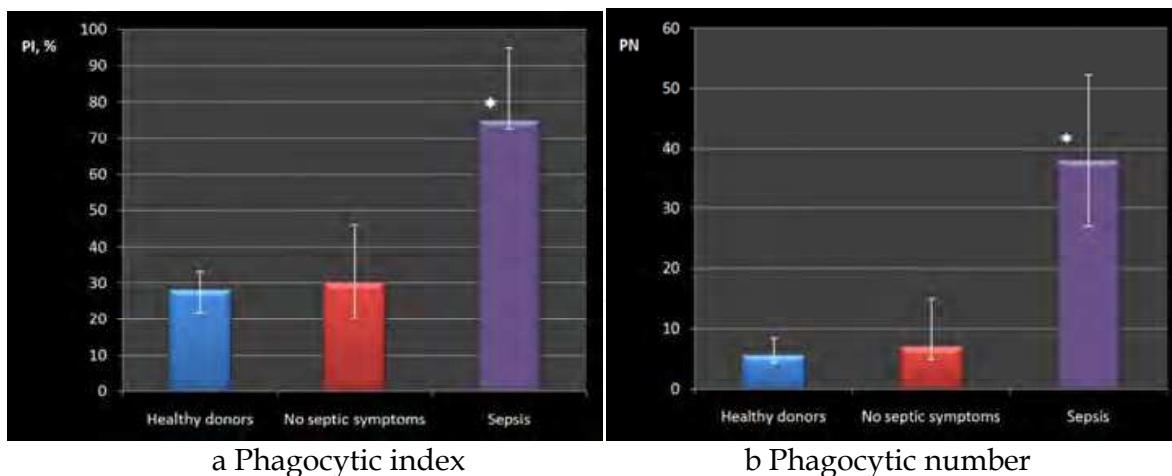
The results of our studies showed that cancer patients with sepsis have a significant increase of natural killer (NK) cells activity as compared with cancer patients having no sepsis or healthy volunteers. These data comply with results of other authors who demonstrated an enhanced function of NK in patients with sepsis (Giamarellos-Bourboulis E.J. et al., 2006, Yoneda O. et al., 2000). The observed phenomenon seemed to be associated with the enhanced rate of IL-12 in blood serum of patients with severe sepsis or septic shock due to the fact that IL-12 stimulates NK and T-killer cells cytotoxicity as a result of secreting molecules involved in cytolytic reactions (gransymes A and B) (Zeerleder S., et al. 2005).

Neutrophils are the first line of protection against acute infections and play an important role in pathogenesis of sepsis (Segal A.W. , 2005). On the one hand they are major players in eliminating infectious microorganisms, on the other hand – an excessive release of oxidants and proteases by neutrophils leads to damaging organs and tissues. Neutrophils are involved both in inflammatory processes and natural immunity effects migrating to the site of infection or inflammation to eliminate infectious agents. Besides that they produce signals about invasion of a foreign agent to alert effectors of innate immunity. These signals induce activation of other cells, such as, monocytes/ macrophages as well as epithelial and mast cells and trombocytes. On activation neutrophils generate various chemotaxic factors attracting macrophages. Because of their common origin neutrophils and macrophages have common functions (phagocytosis, similar behavioral kinetics in infectious and inflammatory process, anti-microbial and immunomodulating functions). Activated neutrophils releasing chemokines stimulate and recruit to the inflammation site monocytes and macrophages and may effect on macrophage differentiation into pro- or anti-inflammatory subtype (type I or type II macrophages). In addition to release of pro-inflammatory cytokines neutrophils also secrete reactive oxygen radicals that induce acute tissue destruction, such as lung destruction in acute reactive distress syndrome (ARDS) or pneumonia (Kumar V. et al., 2010). Besides phagocytosis and secretion of anti-bacterial molecules neutrophils form so-called extra-cellular traps. Extra-cellular traps are formed from the decondensated chromatin and the contents of some granule, as well as from the cytoplasmic proteins and can interact both with gram-negative and gram-positive bacteria leading to destruction of virulent factors and killing bacteria. However the excessive reaction of innate immunity following bacterial infection may lead to immune suppression in the end. Part of this condition is impairment of neutrophil phagocytic activity, which is the major component determining the status of anti-infectious defense (Kumar V. et al., 2010, Giamarellos-Bourboulis E.J. et al., 2010, Volk H.D. et al., 1999).

Patients with sepsis and the background of neutrophil sequestration can often develop complications in tissues, such as ARDS, and excessive activation of neutrophils is associated with lung destruction (Kumar V. et al., 2010, Giamarellos-Bourboulis E.J. et al., 2010).

There is a number of data that demonstrate long-term cellular over-production of pro-inflammatory cytokines (IL-8, TNF α , IL-6, IL-1 β) in cancer patients with sepsis, which can effect neutrophil functions (Martin C. et al., 1994, Zhang B. et al., 1998, Frieling J.T.M. et al., 1995, Barber M.D. et al., 1999, Rigato O. et al., 1996, Segal A.W., 2005). The results revealed that in most cases the phagocytotic activity of neutrophils of cancer patients with sepsis (phagocytic index and phagocytic number) were higher than those of healthy volunteers (in 2,6 and 6,3 times, respectively) (Fig. 3a,b, Fig.4 a,b). This phenomenon may be the results of increased production of pro-inflammatory cytokines, in particular IL-8: key cytokine

involved in recruitment of neutrophils into the inflammation site and stimulating their function (Hammond M.E. et al., 1995).



*– values that have reliable difference from those of healthy volunteers ($p < 0,05$).

Fig. 3. Parameters of phagocytosis rate of blood granulocytes in cancer patients with sepsis and patients with no septic symptoms in comparison with healthy volunteers (median, 25%÷75%).

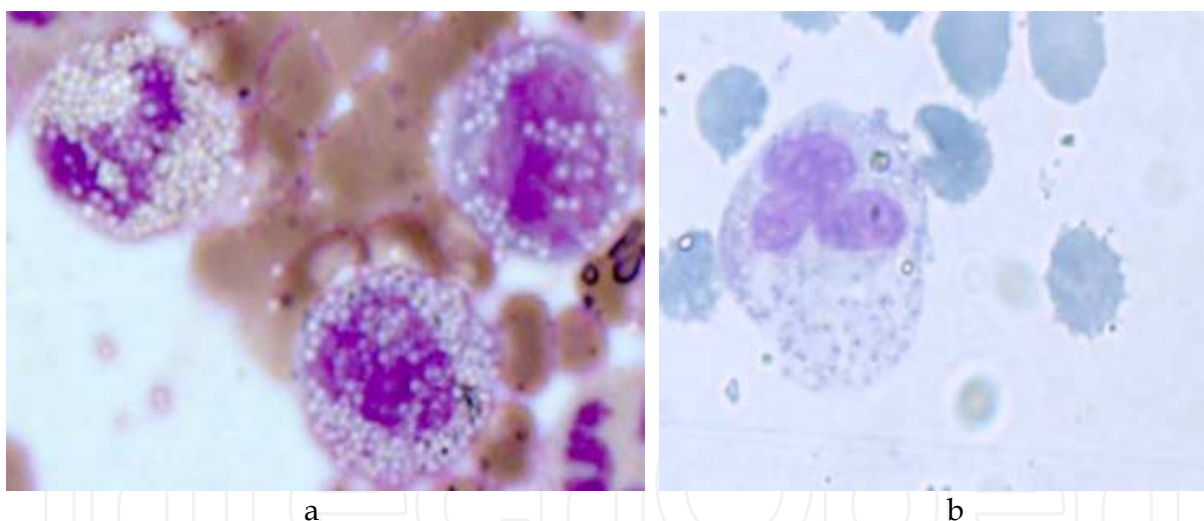


Fig. 4. Microphototos of neutrophils in peripheral blood of healthy volunteers (a) and cancer patient with sepsis (b) after incubation with latex particles ($t=40$ min).

Patients with sepsis have a significant increase in activation of oxygen dependent mechanisms of phagocytes as compared to those of patients with no complications or healthy volunteers (5-fold and 15-fold, respectively) that points to a high rate of activation of intracellular bactericidal systems when there is septic process (Fig. 5).

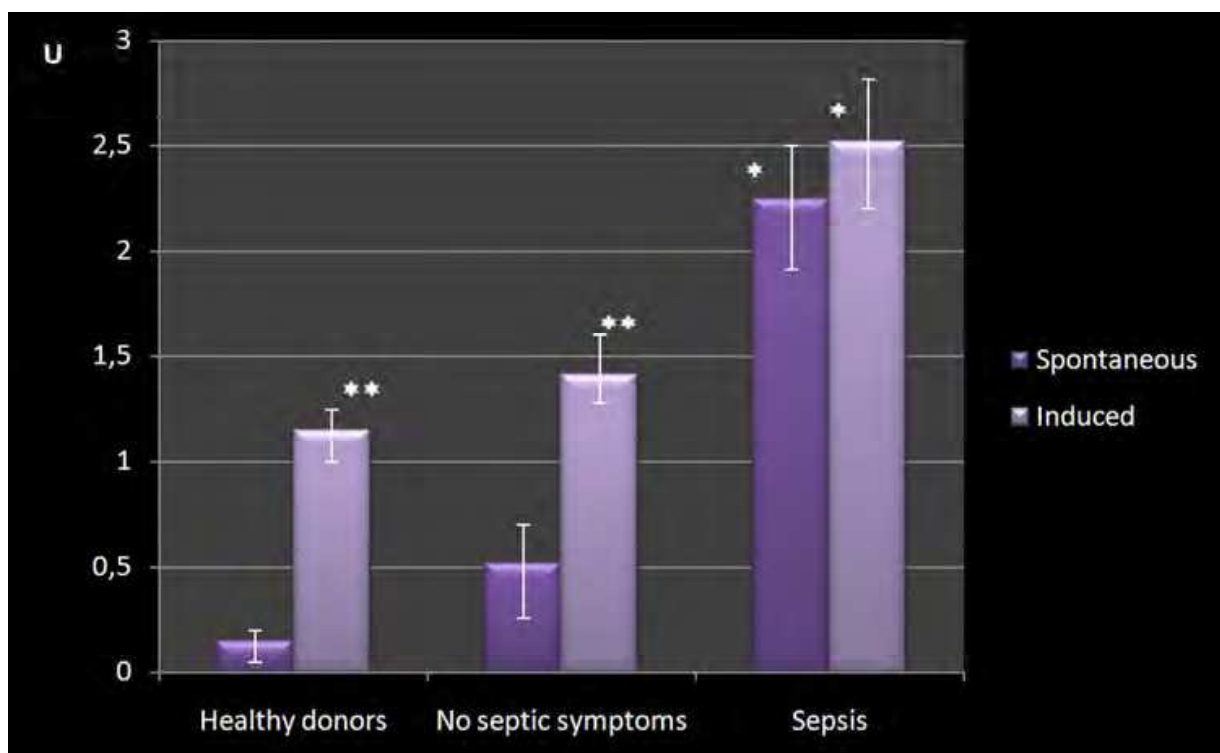
Hydrogen peroxide combined with myeloperoxidase (enzyme of primary neutrophil granules) and halogen ions forms an effective bactericidal system that kills bacteria by halogenation of the cellular wall (Zychlinsky A. et al., 2003). But phagocytes release these endogenous active substances into the inter-cellular medium so that they also destroy self-

tissues and thus they become involved in developing organ dysfunction or MODS (Thomas S. et al., 2004).

Previous studies suggest that the basis for MODS in critical conditions is the impairment of vessel endothelium, which was the result of active function of immune competent cells induced by microbial products. Therefore super-activation of effectors of innate immunity (neutrophils, natural killers) may be considered as an important link in pathogenesis of organ or multi-organ dysfunction syndrome.

Excessive reaction of innate immune system after contact with bacterial infection can lead to immune suppression. A part of this condition is the disorder in phagocytic function of neutrophils, which to a high extent determines anti-infectious defense (Volk H.D. et al., 1999, Alves-Filho J.C. et al., 2010, Giamarellos-Bourboulis EJ et al., 2010).

One of the results of the developing immune suppression in patients with sepsis can be decreased number of lymphocytes that is associated with their sequestration in the inflammation site or their apoptotic death as a result of the excessive production of pro-apoptotic factors. Clinical studies showed marked T-cell lymphopenia with its maximum within a few days. Absolute and relative number of CD4+ and CD8+ T-lymphocytes reduces. At the same time percentage of B-lymphocytes in the peripheral blood goes up (Murphy R.&DeCoursey T. E., 2006, Holub M. et al., 2000). Essential alterations were observed in NK examination (Emoto M. et al., 2002, Kerr A.R., et al., 2005).



*- values that have reliable difference from control ($p < 0,05$);

**- results of the induced NB-test reliably different from the results of spontaneous NB-test ($p < 0,05$).

Fig. 5. Rate of metabolic activity of neutrophils in peripheral blood of cancer patients in comparison with those of healthy volunteers in spontaneous and induced NB-test (nitroblue test) (median, 25%÷75%).

Peripheral blood NK number enhances at the early stage of sepsis in patients with sepsis (Giamarellos-Bourboulis E.J. et al., 2006), while in patients with septic shock their relative number decreases (Holub M. et al., 2000).

5. Apoptosis of the immune cells after trauma

Apoptosis of various immune cells is an important part of immune suppression development in response to an emergency situation (trauma, burns, infection). Suppression of active immunity due to the death of monocytes, macrophages and lymphocytes can enhance risk of opportunistic infections. Moreover, a higher rate of apoptosis in lymphoid tissues and parenchyma organs may lead to disorders in cellular homeostasis and the following inadequate response of the organism as a whole including development of MODS.

Clinical and experimental studies of trauma and burns showed that enhanced production of endogenous mediators of inflammation (heat shock proteins, free oxygen radicals, NO, TNF, IL-1 and IL-6) could activate signaling pathways of apoptosis in different immune cells. Increased expression of apoptotic markers on T-cells (Fas and FasL) was observed in patients who underwent surgery that makes reason for lymphopenia leading to a higher risk of post-surgical infections. However, some authors reported about decrease of apoptotic marker on leukocytes in sepsis and SIRS (Härter L. et al., 2003, Sayeed M.M., 2004, Papathanassoglou E.D.E. et al., 2005, Jimenez M.F., et al. 1997, Lee WL & Downey GP. , 2001). The expression level of this marker on neutrophils correlates with the severity of the inflammation (Fialkow L. et al., 2006). Apparently, alterations in apoptosis regulation as the process responsible for the elimination of fading cells play an essential role in pathogenesis of sepsis and multi-organ dysfunction syndrome (Pieroza P. et al., 2006, Mahidhara R. et al., 2000).

6. Platelets in sepsis

Platelets may be considered as a linking chain between innate immunity and homeostasis. Activated platelets can form clusters in blood circulation system that leads to thromboses and their sequestration in microcirculation often leads to disseminated inter-vessel blood coagulation.

Systemic capillary thrombosis in situation of inter-vessel blood coagulation is one of the reasons for multi-organ dysfunction. Moreover, extended and long-term activation of the coagulation system results in exhausted factors of coagulation and platelet function, which causes increased bleeding.

7. Immunoglobulins

Imbalance of humoral immunity that develops in sepsis presents quantitative and qualitative changes in serum immunoglobulins. A lot of authors report about reduction of immunoglobulins A, G, M and their subtype levels in SIRS (Kyles B.D.M. & Baltimore J., 2005, Tabata N. et al., 1995). The results of a prospective study (Dietz S. et al., 2010) of 543 patients with sepsis demonstrated that half of them had physiological normal IgG level in peripheral blood (6,1-11,9 g/dL). However intra-venous infusion of immunoglobulins in

patients with systemic inflammatory processes is widely used (Berlot G. et al, 2007, Jenson H.B., 1998, Pildal J.& Gotzsche P.C., 2008). On the other hand, some authors state that there was no reliable increase of survival in patients with sepsis after treatment with exogenous immunoglobulins (Alejandria M.M. et al., 2002, Werdan K., 1999).

8. Immunological imbalance in patients with sepsis

At present there is a standpoint of the massive inflammatory reaction as a result of systemic release of cytokines that is the basic cause for MODS (Goris J.A. et al., 1985). A MODS is the result of endothelial cell damage, impairment of vessel penetrative capacity, micro circular disorders with developing cellular hypoxia and finally, cell apoptosis with the release of immune or necrotic proteins. Kidneys and gastro-intestinal tract are highly sensitive to micro-circular disorders, which lead to necrosis of renal tubules that enhances concentration of serum creatinine, develops oliguria or anuria and necrosis of intestine fringes. Excessive inflammatory reaction may change to areactivity that leads to immune suppression (and even to immunological paralysis) and joining secondary infection. Pathological morphological analysis often cannot detect correspondence between histological results and the grade of organ dysfunction registered in patients who died from sepsis. The number of dead tissue cells of heart, kidneys, liver and lungs can be insignificant to reflect the marked organ dysfunctions. Apparently, most symptoms of organ dysfunctions in patients with sepsis can be due to "cell hibernation" or "cell stunning" in the way it happens in myocardial ischemia (Sawyer DB & Loscalzo J., 1985). Reactions that are observed in septic conditions can be also seen in other pathological processes that are not directly linked to effects of microbes or their products, such as trauma, shock, advanced surgical interventions. Therefore the correct definition of sepsis is crucial because different approach to understanding sepsis leads to different treatment strategy (primarily, anti-bacterial) and directly effects the outcome. Biological response to microbial components at the beginning of SIRS and sepsis is considered to be immunological reaction of the body in order to reduce the number of pathogens. However unrestricted and excessive production of pro- and anti-inflammatory mediators plays the major role in pathogenesis of sepsis and MODS. Therefore treatment of sepsis should involve control of mediators of inflammatory cascade. Microbial components (such as endotoxin, etc.) and other mediators of inflammation (cytokines, chemokines, leukotriens, thromboxanes, platelet activating factor) that induce systemic inflammatory syndrome should be eliminated at the early stage of sepsis. Some authors proposed restriction of excessive activation of immune system of patients with sepsis by inhibiting various elements of inflammatory cascade. Monoclonal antibodies against LPS and TNF and other biological regulatory factors were offered to achieve the desired effect. However randomized clinical studies did not show clinical effectiveness of such agents (Vincent J.-L.&Abraham E., 2006). Another promising approach is the use of selective haemosorption with LPS-absorbers that allow elimination of a large part of bacterial toxins and inflammatory mediators from patient's peripheral blood.

9. Haemosorption with LPS-adsorber for elimination of triggers and mediators of inflammation in patients with sepsis and SIRS

Endotoxin (lipopolysaccharide, LPS) is well known as the main biological substance causing Gram-negative septic shock. The lack of clinical success in anti-endotoxin therapies with

antibodies determined the development of extracorporeal methods aimed at reducing the circulating endotoxin level by adsorption. Theoretically such procedures could prevent progression of the systemic inflammatory reaction due to the elimination of inflammation trigger factors and mediators (cytokines, bacterial exo- and endotoxins) from the patient's body. The necessity of eliminating a wide spectrum of substances characterized by different physical and chemical features from blood stipulates the application of non-selective and non-specific methods such as haemosorption. In current clinical practice some devices for haemosorption are used as specific (LPS) adsorbers. Launched in 2006 the Alteco® LPS Adsorber (Alteco Medical AB, Sweden; class IIa medical device) is based on a tailor-made synthetic peptide which is non-toxic and adsorbs endotoxin selectively in a recommended single 2-h treatment with a blood flow of 100–200 ml/min and activated clotting time of ≥ 180 s (information provided by the manufacturer).

Data available confirmed an effective reduction in the LPS level in the patients' blood after this procedure (Yaroustovsky M, 2009, Andersen T.H., 2009). In particular, Kulabukhov VV et al. demonstrated almost total elimination of LPS from the patient's blood (from 1.44 EU/ml before treatment to 0.03 EU/ml post treatment) (Kulabukhov VV., 2008). This effect was accompanied by a reduction in procalcitonin and inflammatory cytokines levels. Also, an obvious improvement was observed in the patient's haemodynamics.

The same results were shown in the work of T. Ala-Kokko et al. (T. Ala-Kokko, 2009). The mean total duration of vasopressor infusion was 46 h shorter in the treatment group compared with the control group (95% CI, 104–12 h, $p = 0.165$), with an average vasopressor requirement period of 17.4 ± 6.8 h (95% CI, 5.8–23.8 h) following the start of adsorption treatment. The level of LPS decreased in all cases except in one study patient and all were without vasopressors at 24 h. The decrease in the Sequential Organ Failure Assessment (SOFA) score was 3.4 ± 1.7 from baseline to 24 h after the treatment. The average period of hospital stay was 3.4 days shorter in the treatment group (95% CI, 21.7–14.8 days, $p = 0.881$).

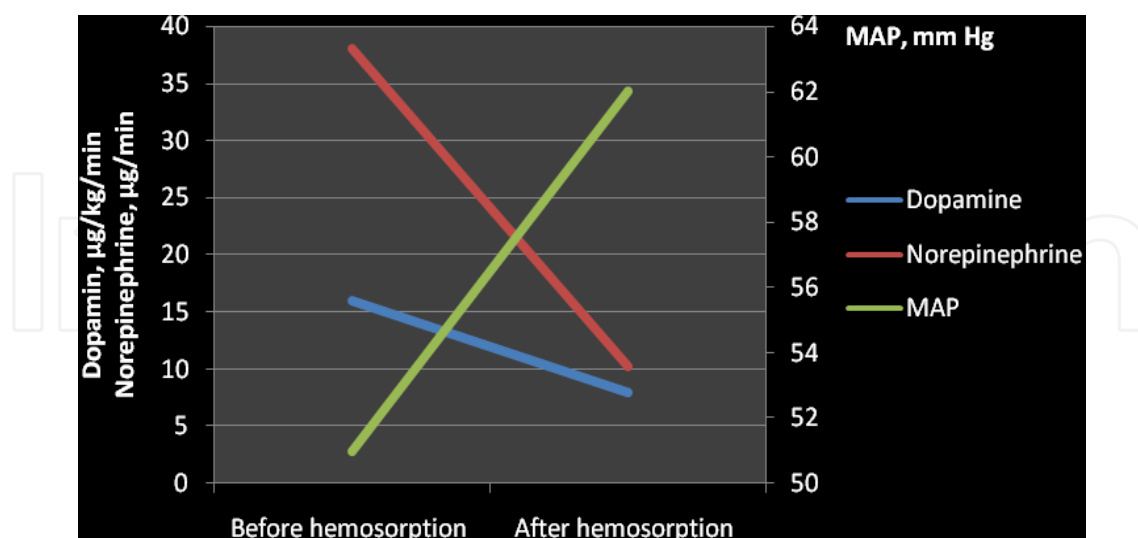


Fig. 6. Inverse correlation of MAP dynamics and vasopressor requirement before and after haemosorption by Alteco.

We studied LPS adsorbers for treating 7 patients with sepsis or septic shock. During the course of extracorporeal detoxification a number of clinical parameters were estimated.

These were temperature, mean arterial pressure (MAP), central venous pressure (CVP), the percentage of available haemoglobin saturated with oxygen (SaO_2), the fraction of inspired oxygen (FiO_2), the partial pressure of oxygen in arterial blood (PaO_2), PaO_2/FiO_2 ratio (an index to characterize the acute respiratory distress syndrome), severe hypoxaemia (insufficient oxygen content in blood), the biochemical parameters of blood (lactate, procalcitonin (PCT)), and concentrations of LPS and cytokines in blood. The requirement for vasopressors (Dopamine, Norepinephrine) was also evaluated.

Data shown in Table 2 and Figure 6 unambiguously demonstrated a pronounced tendency towards the oxygen saturation of haemoglobin (SaO_2) and normalization of the oxygen index (decreasing FiO_2 on 22%). This was associated with a rise in MAP and a decrease in CVP. Normalization of cardio-vascular system function led to a reduction in the requirement for vasopressors.

Parameters	Before hemosorption	After hemosorption	p
CVP, mm Hg	16±5.0	12±4.1	>0.05
SaO_2 , %	87±6.1	94±5.9	>0.05
FiO_2 , %	77±32.3	55±15.4	<0.05*
PaO_2/FiO_2	160±70.9	200±54.1	<0.05*
PCT ng/ml	22±14.3	12±6.0	>0.05
Lactate, mmol/l	4.3±1.3	4.5±3.2	>0.05

* Significant difference

Table 2. Clinical parameters before/after haemosorption by Alteco.

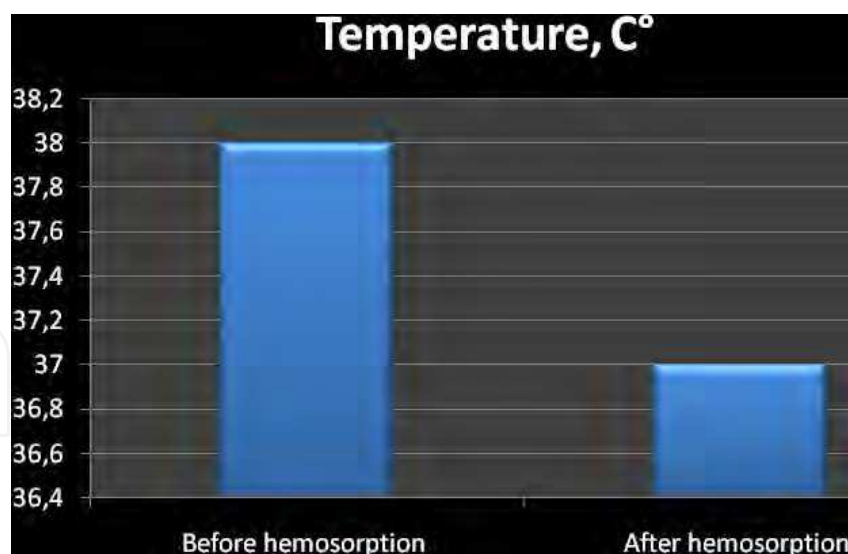


Fig. 7. The body temperature values for patients before and after haemosorption by Alteco.

The significant increase in the respiratory index (PaO_2/FiO_2) after haemosorption evidenced the improvement of oxygen diffusion through the alveoli-capillary membrane.

As a result, normalization of integral indices, such as body temperature and blood PCT level, was observed (Fig.7).

The level of LPS, the key trigger signal for system inflammatory reaction, decreased by a factor of 2 to 3 versus control after haemosorption (Fig.8).

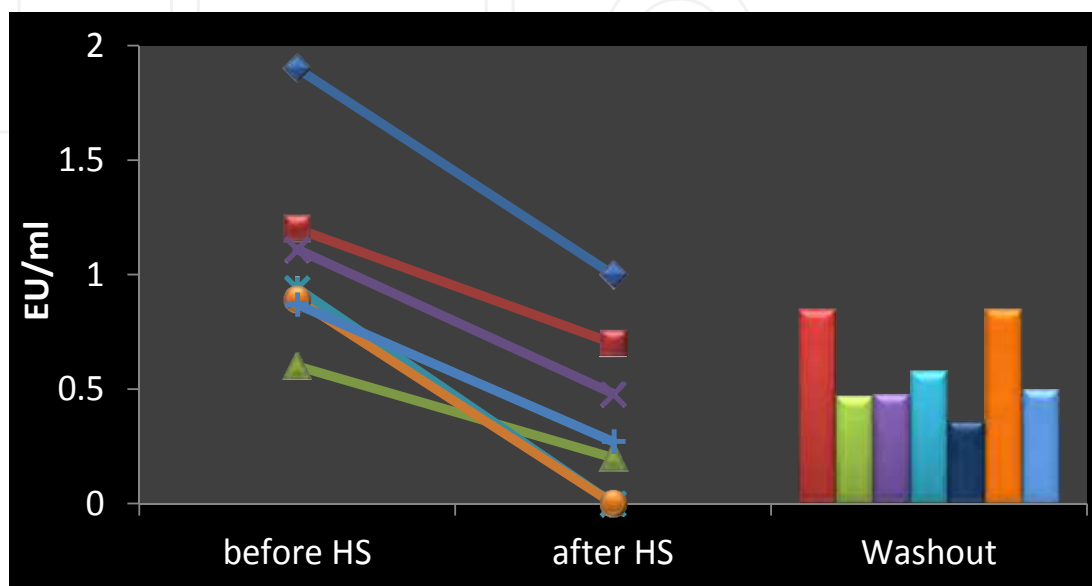


Fig. 8. LPS level in the blood of patients with sepsis before and after haemosorption by Alteco.

As hypercytokinaemia determines the development of SIRS, it seems to be possible that reducing cytokine levels (IL-8, IL-1 β , IL-6, IL-10 etc) in blood may block the generalization of this pathological process or interrupt the cascade of cytokine storm. We studied the influence of haemosorption on the cytokine content in blood (Fig. 9).

Equal portions of sorbent were suspended in equal volumes of physiological solution (0.9% NaCl) and put onto the shaker during temperature control. High levels of some cytokines (IL-6, IL-8, IL-12, INF γ and TNF) were indicated in the supernatant (Fig.9).

We also investigated washouts from a sorbent after the termination of the haemosorption procedure. There were no well-developed specific conditions for the extraction and quantitative estimation of the characteristics of the sorbent.

This approach was especially informative in cases in which the level of analyte was higher in the blood after haemosorption than before the treatment (see examples in Fig. 9). Moreover, an increase in the concentration of some soluble cytokine receptors (sIL-1 II R, sIL-6 R) was observed in patient blood after haemosorption (Fig. 10).

We assumed that this phenomenon was determined by the release of cytokines from their complexes with receptors or proteins during the course of haemosorption.

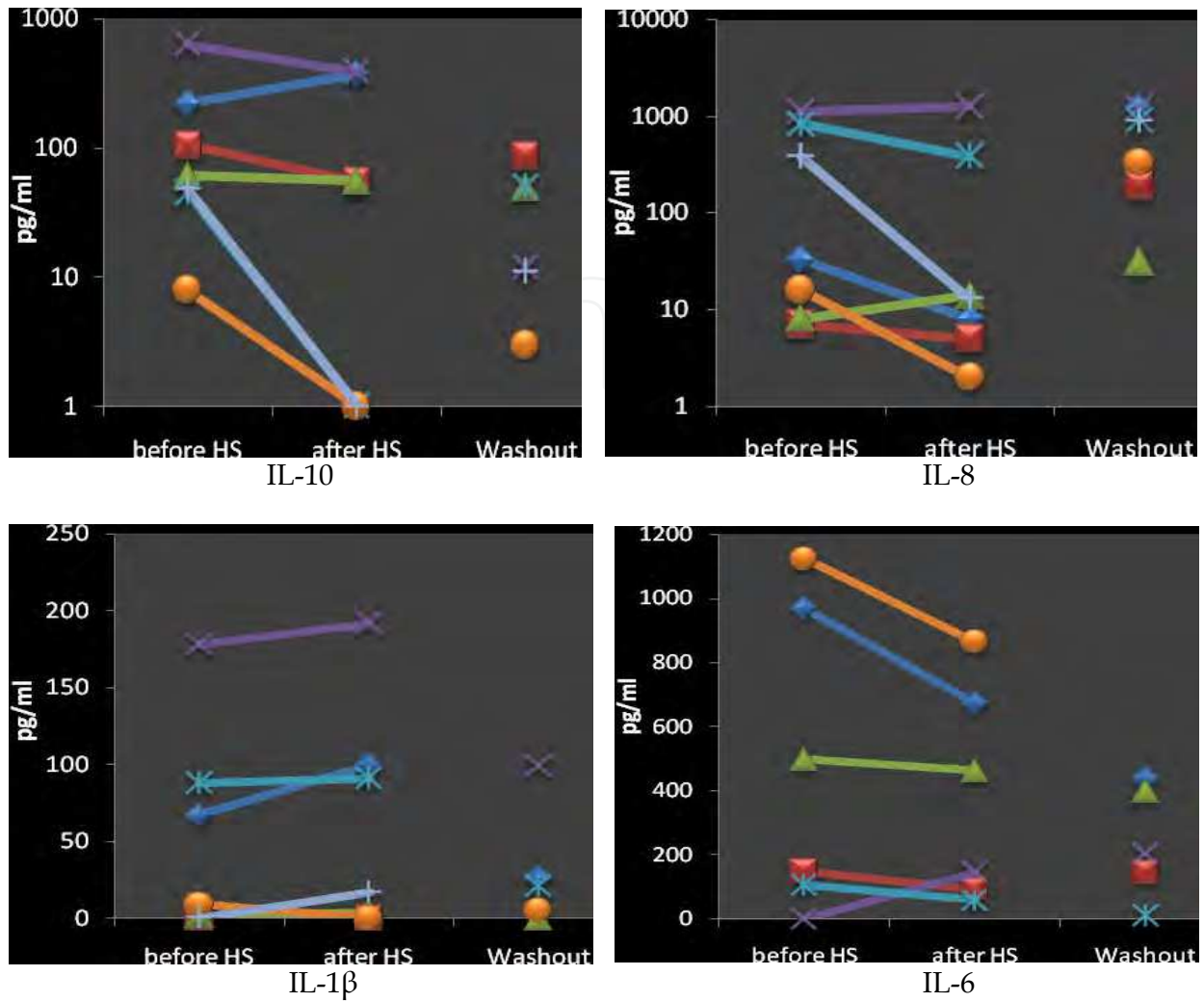


Fig. 9. The levels of cytokines in the blood of patients with sepsis before and after haemosorption by Alteco.

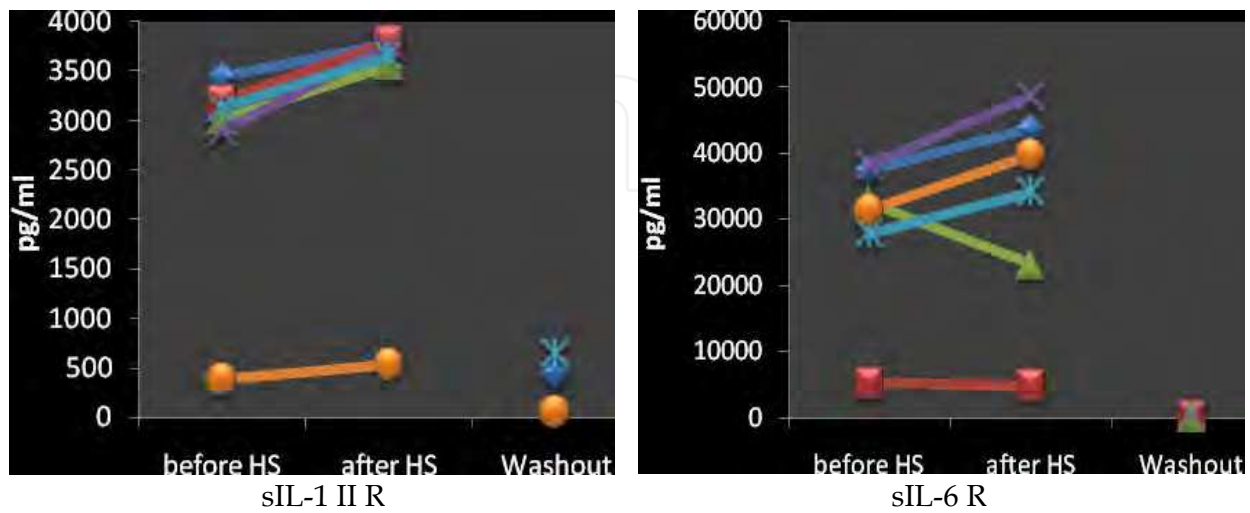


Fig. 10. Serum levels of soluble receptors in the blood of patients with sepsis before and after haemosorption by Alteco.

Our results indicated that low levels of serum cytokines revealed by ELISA did not reflect the real content of these mediators of inflammation in the blood of patients with septic complications. Perhaps a high secretion of cytokines was accompanied by an increase in the expression of congruent receptors, which bound a significant quantity of free cytokines in ligand-receptor complexes capable of dissociation. We showed that extracorporeal detoxification using the Alteco device allowed the elimination not only of free cytokines, but also the majority of bound endogenous bioregulators from cytokine/receptor complexes. Removal of the trigger factor (LPS) along with a wide range of pro- and anti-inflammatory cytokines, and possibly with other inflammation mediators (leukotrienes, thromboxanes, C-reactive protein) led to the interruption of the systemic inflammatory reaction, which was regarded as positive clinical effect of haemosorption for extracorporeal detoxification. Correlation analysis demonstrated a close connection between the concentrations in blood of LPS and TNF α ($p=0.050$), LPS and IL-8 ($p=0.050$). During the study, a 28-day survival of 9 critical patients was 96%, only 1 patient died after the procedure.

Taking into account a high correlation of normalized clinical parameters and the dynamics of LPS level and the serum profile of cytokines, the testing parameters (serum levels of IL-6, TNF α , IL-8) could be considered additional indicators of patient's status during the course of treatment, including methods of extracorporeal detoxification.

We assumed that changes in serum concentrations of cytokines after haemosorption might influence the functional activity of immune cells. Neutrophils and natural killers (NK) play a crucial role in pathogenesis of organ and multi-organ failures in case of sepsis. Our results demonstrated a pronounced tendency towards normalization of the functional activity of these innate immunity effectors after haemosorption by Alteco. Thus, phagocytic number (PN) and phagocytic index (PI) decreased after haemosorption in 1.3 - 2.1 times and 2.1 - 2.6 times, respectively. A reduction in spontaneous neutrophil activity was also observed. This parameter indicates the intensity of oxygen-dependent phagocytosis associated with the release of free radicals destroying the adjacent cells including endothelium. Moreover, the decrease was observed in the super-aggressive non-specific reaction of NK: index of cytotoxic activity (ICA) reduced after haemosorption from 75-90% to 54-58% (normal for healthy volunteers). This effect of normalizing functional activity of neutrophils and NK is likely connected with the elimination of LPS molecules and cytokines from peripheral blood.

Stimulation of immune cells for a long period could lead to exhaustion of their killing activity, resulting in the circulation of leukocytes that are unable to provide defence functions, such as termination of phagocytosis and killing transformed cells. These "ballast" cells do not express apoptosis receptor CD95 on their surface membrane, and consequently they cannot be eliminated from system circulation.

It was shown previously that prolongation of life of leukocytes could produce tissue and organ damage in case of SIRS and sepsis. A change in apoptosis regulation may influence pathogenesis of sepsis and multi-organ failure. We demonstrated the increase in CD45+CD95+ cell number (from 21-24% to 38-40%) after haemosorption. After the treatment, the number of CD45+CD66b+CD95+ neutrophils was higher by 32-42%, which correlated with an increase in the number of phagocytes able to terminate oxygen-dependent phagocytosis. Correlation analysis revealed a strong connection between these parameters ($p=0.0086$).

Therefore, reduction of the functional activity of leukocytes (PN, PI, ICA) to the level of that of healthy individuals and simultaneous increase in CD95+ leukocyte level could be considered a favourable prognostic factor.

The obtained results demonstrated that the LPS adsorber could effectively eliminate a wide range of the factors from peripheral blood (such as LPS, cytokines, etc.), which mediate all the stages of systemic inflammatory reaction in the body. Significant improvement of the performance status of patients with sepsis was observed after extracorporeal detoxification with LPS adsorber. This was the normalization of cardio-respiratory functions and reduction in hyperthermia and vasopressor requirement, normalization of MAP and concentration of gases in peripheral blood.

10. Conclusion

The discussed data and information show that cancer patients with sepsis have an enhanced serum level of LPS as compared to healthy volunteers. There is a close link between a decreased serum level of LPB along with the 10-fold reduction of LPB/LPS ratio and poor prognosis in cancer patients with sepsis. A characteristic cytokine profile of septic condition demonstrated that IL-6, IL-18 and soluble receptor sTNF RI concentrations significantly exceeded those of healthy volunteers and therefore high serum concentrations of IL-6, IL-8, IL-10, sTNF RI, sIL-1 RII, and sIL-6 R could be suggested as markers of sepsis for cancer patients.

In conclusion, triggers and mediators of inflammation secreted by immune cells play a crucial role in pathogenesis of SIRS and sepsis. Management of the inflammatory cascade should be considered an essential part of the complex approach to the treatment of systemic suppurative septic complications.

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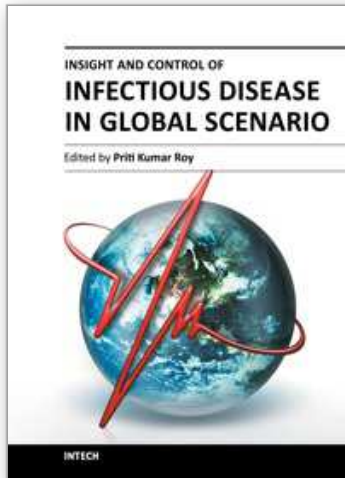
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