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Immune disorders in sepsis and their treatment as a significant problem of modern intensive care

Zaburzenia immunologiczne w sepsie oraz ich leczenie jako istotny problem współczesnej intensywnej terapii

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Summary

Despite the great advances in the treatment of sepsis over the past 20 years, sepsis remains the main cause of death in intensive care units. In the context of new possibilities of treating sepsis, a comprehensive response of the immune system to the infection, immunosuppression, in particular, has in recent years gained considerable interest. There is vast evidence pointing to the correlation between comorbid immunosuppression and an increased risk of recurrent infections and death. Immune disorders may impact the clinical course of sepsis. This applies in particular to patients with deteriorated clinical response to infections. They usually suffer from comorbidities and conditions accompanied by immunosuppression. Sepsis disrupts innate and adaptive immunity. The key to diagnose the immune disorders in sepsis and undertake targeted immunomodulatory therapy is to define the right biomarkers and laboratory methods, which permit prompt "bedside" diagnosis. Flow cytometry is a laboratory tool that meets these criteria. Two therapeutic methods are currently being suggested to restore the immune homeostasis of sepsis patients. Excessive inflammatory response may be controlled through extracorporeal blood purification techniques, in large part derived from renal replacement therapy. These are such techniques as high-volume haemofiltration, cascade haemofiltration, plasma exchange, coupled plasma filtration and adsorption, high-absorption membranes, high cut-off membranes. The main task of theses techniques is the selective elimination of middle molecular weight molecules, such as cytokines. Pharmacotherapy with the use of such immunostimulants as interleukin 7, granulocyte-macrophage colony-stimulating factor, interferon gamma, PD-1, PD-L1 and CTLA-4 antagonists, intravenous immunoglobulins may help fight immunosuppressive immune disorders.

Słowa kluczowe: **sepsis, immunological disorders, diagnosis, immunomodulatory therapy**

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Despite the great advances in the treatment of sepsis over the past 20 years, sepsis remains the main cause of death at intensive care units (ICUs). The mortality rate is approximately 40% [43]. Since the first treatment guidelines for severe sepsis and septic shock were published [10], the key elements of treatment have included early application of the proper antibiotics, sanation of the septic focus and support of the dysfunctional organs. In the context of new possibilities of treating sepsis, a comprehensive response of the immune system to the infection has in recent years gained considerable interest [19]. There is vast evidence supporting the correlation between sepsis-induced immune disorders and the increased risk of secondary infections and of death [18,27].

Cells of the immune system are activated shortly after the onset of the infection, with intense secretion of pro- and anti-inflammatory cytokines. The main task of this response is to capture and eliminate the pathogen. If the secretion of cytokines is controlled, it leads to restoration of homeostasis, also that of the immune system. Sepsis is defined as the host's pathological response to infection. So on the one hand, this may lead to an uncontrolled, excessive inflammatory response with premature death or to a two-stage response, where the initial inflammatory response is followed by exacerbated anti-inflammatory response with late death. On the other hand, an exacerbated inflammatory response may take place, with clear anergy of the immune system cells since the moment the infection factor is activated [19]. This immunoparalysis is the cause of the majority of deaths in the course of sepsis [61].

Varied clinical course of sepsis

Two scenarios of the clinical course of sepsis are usually observed, depending on the degree of the host's response to the infection [9]. One population consists of young or middle-aged patients without comorbidities, usually suffering from non-hospital-acquired infections with highly virulent pathogens (*N. meningitidis*, *S. pyogenes*, *S. aureus*, pneumococci in patients after splenectomy). In this group, due to the excessive secretion of cytokines and the uncontrolled inflammatory response, the clinical course is violent, with high fever, shock resistant to treatment, permeability of blood vessel walls, acute adult respiratory distress syndrome (ARDS), hypercatabolism and disseminated intravascular coagulation (DIC). Laboratory tests of peripheral blood show a significantly increased or radically decreased granulocyte count and severe lactic acidosis. Patients die relatively soon due to the multiple organ dysfunctions being hard to treat. Nowadays, due to contemporary intensive care possibilities, the classic violent clinical course is relatively rare. The other population, comprising patients with reduced clinical response to infection, is a much more frequent phenomenon and a bigger therapeutic challenge. This group usually consists of patients with comorbidities involving immunosuppression (for instance solid tumours and blood cancers, the condition after transplantation of solid organs, autoimmune and systemic diseases, HIV, use of immunosuppressants) [18,27]. Many of these patients have additional risk factors which affect their immune system [9]. They include but are not limited to chronic alcoholism, malnutrition, kidney failure, and liver failure. Another, particularly important, risk factor in this group is advanced age, as it is common knowledge that elderly people have a weaker immune system. This condition is known as "immunosenescence" [40]. In this group, sepsis is usually caused by low-virulence pathogens or opportunistic pathogens (*Acinetobacter*, *Stenotrophomonas*, *Enterococcus*, fungi). As a result of immunosuppression, these patients may suffer from recurrent infections caused by latent viruses. This is confirmed, e.g. by detection of herpes simplex virus (HSV) in upper or lower respiratory airways, with or without the presence of herpes-induced damage to the nasopharyngeal cavity, or by detection of HSV DNAemia or cytomegalovirus viremia in blood [62]. Even though activation of latent viruses rarely leads to the development of organ dysfunction, it is a risk factor for bacterial or fungal infections as it additionally impairs the function of immune system cells. Patients with baseline immunosuppression are often characterised by a "vague," less clear clinical picture of sepsis, with such symptoms as limited mental functions, glucose intolerance, hyperglycaemia, hypothermia, and changes in WBC count or in differential WBC count. Laboratory tests often reveal lymphopenia persisting for over 3-4 days. Death in this patient group usually follows a longer period of illness. Furthermore, in each sepsis case, the host's response to the infection is implicitly impacted by the genetic predispositions and epigenetic changes connected with non-genetic inheritance [42,52].

The diversity of the clinical course presented above does not differentiate the treatment strategy, as the therapy must in any case proceed in accordance with the applicable international guidelines for the treatment of sepsis and septic shock [46]. It is of great importance in the initial management phase, aside from resuscitating the cardiovascular system through intravenous fluid infusion, to reach a microbiological diagnosis and provide antimicrobial treatment.

Immunosuppression mechanisms in sepsis and their identification

Sepsis leads to many disorders in innate and adaptive immunity. The observed phenomena include reduced activity of monocytes, weakened bactericidal functions of neutrophils (adhesion, phagocytosis), apoptosis-induced reduction of effector cells (lymphocytes, dendritic cells), increased myeloid-derived suppressor cell (MDSC) count, increased count of CD4+, CD25+ regulatory T cells (Tregs) [16,19,54].

Table 1. Biomarkers of immune system dysfunctions in sepsis determined according to FCM

Immune response	Assay	Biomarker
Innate	functional testing	↓ ex vivo cytokine production after TLR agonist stimulation
	plasma cytokines	↓ IL-10
	cell surface marker expression	↓ mHLA-DR, CD14, CD86, GM-CSFR, CX3CR1
	apoptosis	↓ CD14, depolarized mitochondria
Adaptive	functional testing	↓ proliferation after antigenic or nonspecific stimulaion
	cell surface marker expression	↓ inhibitory receptors: PD-1, CTLA4, CD47 ↓ co-activator receptors:CD28, CD3 ↓ % CD4+CD25+ regulatory T cells
	apoptosis	↓ T-cell count ↓ Annexin V staining ↓ Bcl2 expression protein

FCM – flow cytometry, TLR - Toll-like receptor, IL-10 - interleukin 10, mHLA-DR - human leukocyte antigen-DR expression on circulating monocytes, CD14 - co-receptor for the detection of bacterial lipopolysaccharide, CD86 - is a protein expressed on antigen-presenting cells, GM-CSFR - granulocyte macrophage colony-stimulating factor receptor, CX3CR1 - CX3C chemokine receptor 1, PD-1 – programmed death cell-1, CTLA4 – cytotoxic T-lymphocyte antigen-4, CD47 - integrin associated protein, Bcl2 – B-cell lymphoma 2.

The power of immunosuppression in sepsis may be equal to that of the immunosuppressive therapy. This is confirmed by the results of the observational study published by Manez R *et al.* [31]. The authors present a group of post-liver-transplantation patients who developed life-threatening infections. Discontinuation of immunosuppressive drugs did not result in the transplant being rejected. Only few of these patients required re-application of immunosuppressants due to moderate symptoms of transplant rejection. And in these cases it was possible to reduce the dose of immunosuppressants to 50%.

The key to targeted immunomodulatory therapy in sepsis is to define the right biomarkers and laboratory methods to reach a prompt "bedside" diagnosis of the comorbid immune system dysfunction, available 24 hours a day 7 days a week (system 24/7) [37]. Such diagnostics would make it possible to individualise the treatment, *e.g.* through the application of immunostimulation in patients with immunosuppression. Flow cytometry (FCM) is a laboratory tool that can meet this criterion [30]. This method permits analysing such biomarkers as the monocyte human leukocyte antigen-DR (HLA-DR) expression, the bactericidal functions of neutrophils or the percentage of the circulating CD4+, CD25+ regulatory T cells (Tregs). Currently, monocyte HLA-DR expression seems to be the most credible biomarker in the evaluation of the immunological state of septic patients. Low HLA-DR expression, and in particular the inability to rebuild it, points to immunoparalysis, which increases the patient's proneness to infections with opportunistic pathogens and gives bad prognosis [25]. Its normal activity ranges from 70 to 100%. Low HLA-DR expression correlates with a reduced ability of monocytes to present the antigen and produce pro-inflammatory cytokines [12,28,35,37].

As has been mentioned above, sepsis may entail dysregulation of the bactericidal function of neutrophils. These functions are regulated through a number of receptors. A very important role is played by two of them – the complement receptor 3 (CR3) and a complex consisting of dectin-1 and of Toll-like 2 and 6 receptors (TLR2/6). The first piece of evidence pointing to dysregulation of the bactericidal function of neutrophils comes from experimental studies. They revealed a disrupted phagocytic activity of neutrophils during sepsis with inhibited, phagocytosis-induced, intracellular production of reactive oxygen species (ROS) [23]. There are also many reports describing the disruption of the bactericidal functions of neutrophils in septic patients, pointing to a defect of CR3 or the dectin-1/TLR2/6 receptor complex [16,54].

Sepsis is accompanied by an increased percentage of Treg lymphocytes [37,58]. Tregs produce interleukin 10 (IL-10) and the transforming growth factor beta (TGF-β); they inhibit the antigen-presenting cells, B lymphocytes, T helper cells (Th), cytotoxic T cells (Tc) and natural killer cells (NK). A Treg percentage increase was noted in experimental studies on animals with multibacterial sepsis and

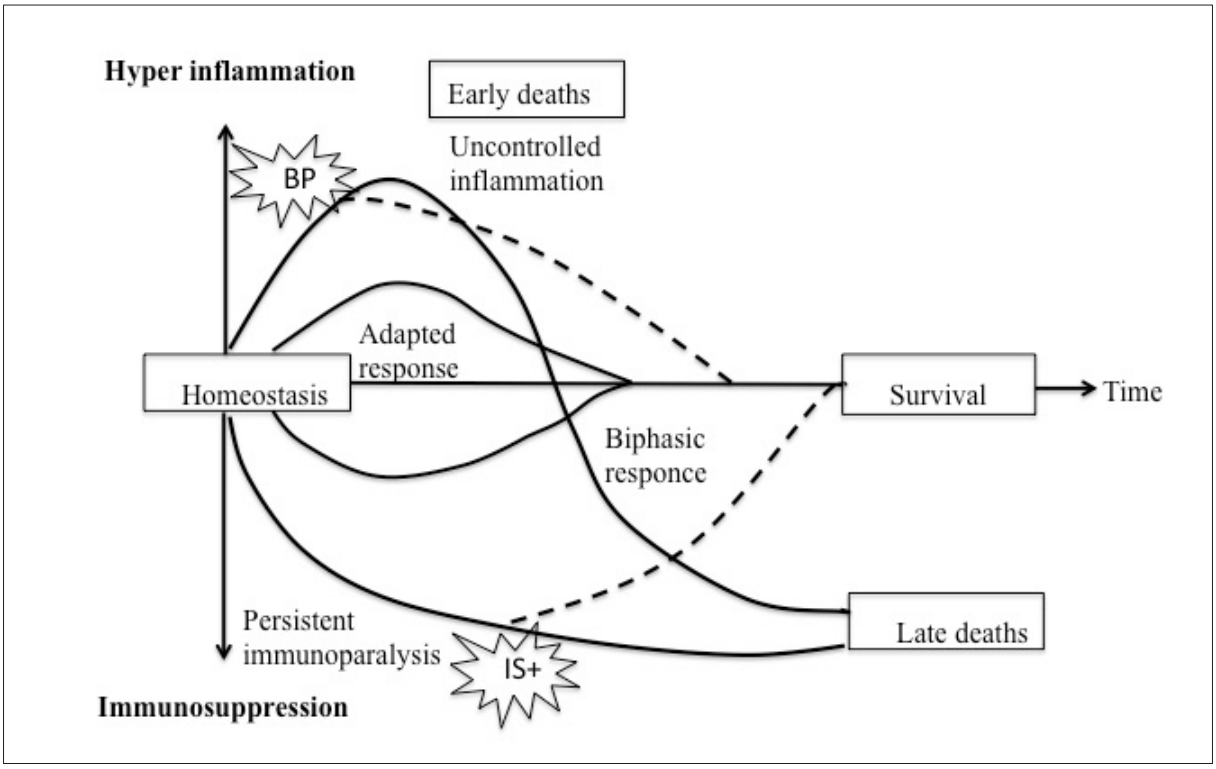

Fig. 1. Types of the host's responses during sepsis and the impact of immunomodulatory treatment (according to Girardot et al.) [13]
Continuous lines: possible types of immune response; *broken lines:* possible treatment effects; BP: blood purification methods; IS+: immunostimulants

on patients in septic shock [58]. It was also observed that the increase of the Treg percentage in the blood of patients in septic shock was correlated with reduced proliferative response of leukocytes to mitogen stimulation [57]. This proves that Tregs may play a central role in the development of immunoparalysis, and their percentage value can be measured with a reliable biomarker of lymphocyte dysfunction in sepsis. In the blood of healthy people, the Treg population represents 6-8% of all CD4+ T cells [60]. In addition to the ones presented above, there are other biomarkers that can be determined with FCM to identify the immune system dysfunctions in terms of non-specific and specific immune response [55,60]. They include: function tests, determination of serum cytokine level, measurement of expression of various markers on the surface of cells or determination of the extent of apoptosis (Tab. 1). The studies to be conducted in the upcoming years will show which of these biomarkers, or possibly which panel thereof, determined via bedside tests using standardised FCM protocols, will be applied in daily clinical practice.

Assisted immunomodulatory treatment methods

Two therapeutic methods are currently being suggested to restore the immune homeostasis of septic patients [13]. An excessive inflammatory response can be controlled through extracorporeal blood purification, while immunostimulants may help fight such immune system disorders as immunoparalysis (Fig. 1).

A. Extracorporeal blood purification methods

A few extracorporeal blood purification methods, in large part derived from renal replacement therapy (RRT), were applied to modulate the immune response during sepsis. Elimination of inflammatory mediators, such as IL-1, IL-6, TNF-α from the blood system may limit their cytotoxic activity and improve the migration of leukocytes to the septic focus. These methods may also modify the immune cell phenotype, which is severely disrupted during sepsis [49].

High-volume haemofiltration

High-volume haemofiltration (HVHF) is defined as application of ultrafiltration greater than that used to support renal function, i.e. >50 ml/kg/hour. Large and very large ultrafiltration flows were used to increase the elimination of medium-molecular-mass molecules, such as, e.g. cytokines [50].

For a long time HVHF was the most frequently used blood purification method, supported by the results obtained in experimental tests on animal models and in pre-clinical studies. In the experimental model of cholangiopancreatitis, HVHF helped restore the correct expression of immunoparalysis markers. A beneficial impact of this method on the mortality rate was also implied [63]. However, it must be stressed that a

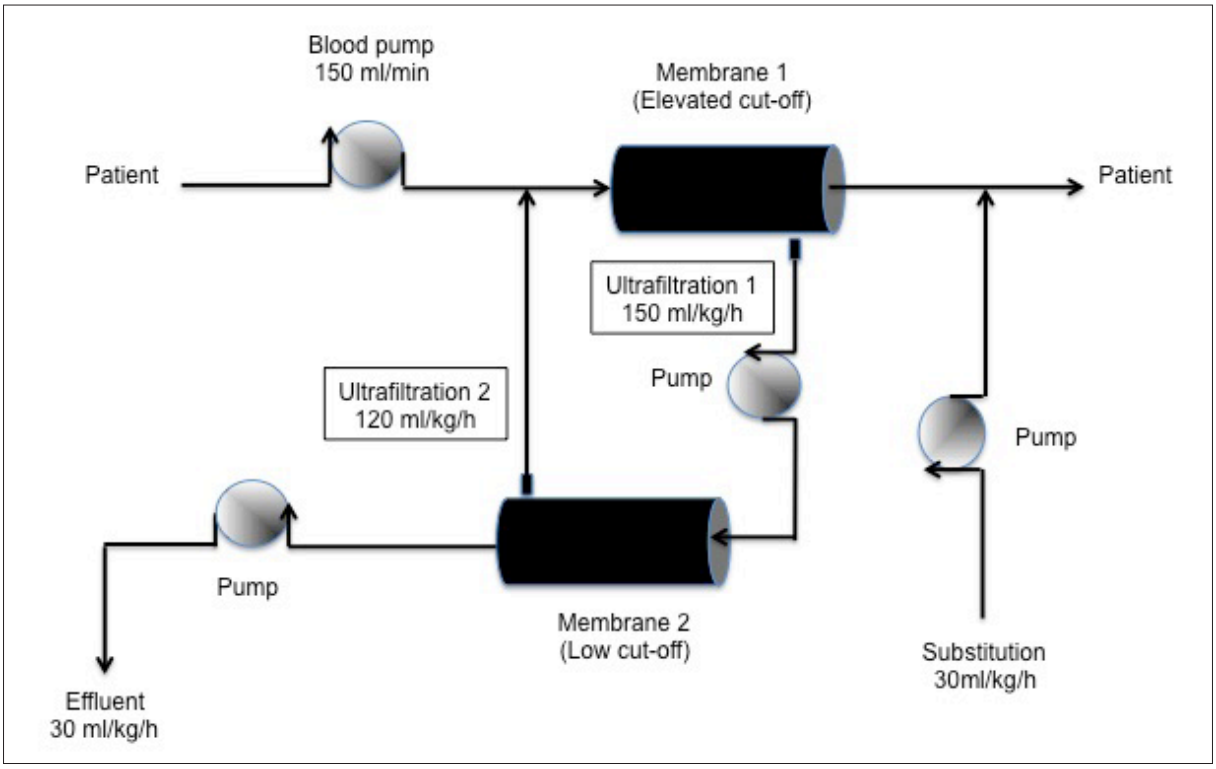

Fig. 2. Cascade haemofiltration chart

randomised IVOIRE study which compared ultrafiltration of 35 ml/kg to ultrafiltration of 70 ml/kg in patients in septic shock suffering from acute kidney injury (AKI) did not reveal any benefits in terms of reduced mortality rate [21]. Based on two new meta-analyses supporting these negative results [3,7], the IVORE challenges the application of HVHF in septic patients.

Cascade haemofiltration

HVHF has significant limitations. One of them is the considerable loss of low-molecular-mass molecules, such as antibiotics, nutrients, microelements and vitamins. With two different haemofilters, the cascade circuit may help avoid these flaws. It is a concept that makes it possible to eliminate medium-molecular-mass molecules and lets low-molecular-mass molecules return to the patient's blood. The first filter with an increased-cut-off membrane channels an ultrafiltrate (ultrafiltrate 1) containing low- and medium-molecular mass molecules to another filter. The other filter, with a low-cut-off membrane, allows the low-molecular-mass molecules to return to the patient, at the same time "selectively" eliminating – together with the ultrafiltrate (ultrafiltrate 2) – the medium-molecular-mass molecules, such as cytokines (Fig. 2). In the animal septic shock model, the above method made to possible to reduce the demand for epinephrine and improve the clinical parameters when compared to the standard HVHF [48].

Plasma exchange

Plasma exchange involves removal of the patient's own plasma, which is replaced by infusion fluids. This method, at least theoretically, may be effective in removing cytokines from the patient's blood. Such tests were already conducted at an early stage of gram-negative bacterial infections, and the results were auspicious [15]. Cytokine removal through plasma exchange may reduce the level of inflammatory markers in sepsis and in organ failure [45]. In one randomised study, plasma exchange improved the survival rate of patients in septic shock when coupled with conventional treatment, but this only applied to a subgroup of patients with intraabdominal infections [5].

Haemoperfusion

Haemoperfusion, also known as hemoadsorption, involves using materials with high adsorptive properties. Blood circulates in direct contact with the adsorptive surface, which attracts the molecules through hydrophobic, ionic and van der Waals interactions. From there, the high-molecular-mass molecules, which exceed the cut-off of standard high-flux haemofilters, may be removed from the blood by being bound to the adsorptive surface [13]. The technical problems connected with the biocompatibility of adsorptive materials have already been solved. The limitations of this method consist in haemoperfusion not being a renal replacement method [50].

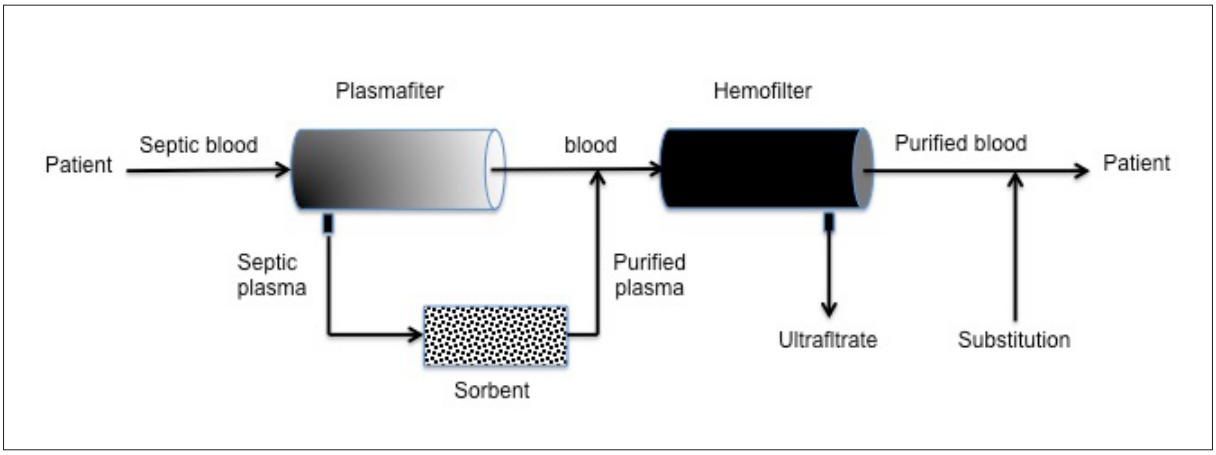

Fig. 3. Coupled plasma filtration and adsorption chart

In a meta-analysis conducted in 2013, evaluation of the impact of blood purification on the mortality rate in sepsis was based mostly on studies carried out in Japan. These studies assessed polymyxin B haemoperfusion [64]. The material has broad applications, in particular in the treatment of infections inducted by gram-negative bacteria. Results of the EUPHAS randomised study were published in 2009. In that study, the respiratory and circulatory function as well as the prognosis in patients with severe sepsis in the course of intraabdominal infections improved after the application of polymyxin B haemoperfusion [8]. The results obtained in the ABDO-MIX study did not confirm the previous results [39]. The objective of that multicenter randomised study was to evaluate the impact of polymyxin B haemoperfusion on the mortality rate of patients in septic shock in the course of peritonitis. No statistically significant differences were observed between the experimental group (polymyxin B haemoperfusion) and the control group, treated conventionally. Even a trend towards higher mortality was noted in the experimental group. A randomised EUPHRATES study is currently being conducted on patients in septic shock, which may provide additional information about the potential usefulness of polymyxin B haemoperfusion [24]. Furthermore, haemoperfusion was also tested with other adsorbents, e.g. divinylbenzene. In *ex vivo* conditions, this material proved to be highly capable of removing activated cells of the immune system from blood and modifying the cytokine expression profile [49]. In the animal septic shock model, application of the above adsorbents was connected with reduced IL-6 and IL-10 concentration and longer survival of the animals [41].

Coupled plasma filtration and adsorption

Coupled plasma filtration and adsorption (CPFA) is a new method which may join the group of extracorporeal blood purification methods [20]. First, plasma is isolated from the patient's whole blood through a proper filter. Afterwards, it is purified, slowly going through the adsorptive material. Then the plasma returns to the patient's blood and is channelled to the haemofilter of a standard RRT (Fig. 3). This is a called a "hybrid" method of standard continuous RRT [51].

In a pilot study conducted in patients with severe sepsis and multiple organ dysfunctions, CFPA was more effective than HVHF in reversing immunoparalysis. This method particularly improved the monocyte HLA-DR expression and restored the lipopolysaccharide (LPS)-induced production of the tumour necrosis factor-α (TNF- α) [32]. In 2014, results of the COMPACT-1 study were published, where the CPFA was coupled with standard treatment of septic shock. This study encountered some problems with system clotting, which limited the volume of the plasma to be purified. However, a correlation was observed between the mortality rate and the volume of the purified plasma. The mortality rate was lower in the subgroup of patients who received a "higher" CFPA dose than in the control group [29]. A COMPACT-2 study (NCT 01639664) is currently being conducted to confirm the observations from the COMPACT-1 study regarding patients in septic shock. The COMPACT-2 study uses regional citrate anticoagulation to prevent system clotting, which is to make high CPFA doses (>0.2 l/kg/day of plasma) possible.

High-absorption membranes

The high-absorption membranes used in RRT can be modified to become an additional blood purification device [17]. For instance, adding a positively charged polymer to a classic polyacrylonitrile membrane improves its adsorptive properties for LPS and proinflammatory cytokines. In the animal septic shock model, 6-hour application of HVHF with the above membrane improved the circulatory function when compared to a standard membrane [47].

High-cut-off membranes

Other membrane properties may be modified as well. Increasing membrane cut-off may permit removing

a wider range of medium-molecular-mass molecules. Such membranes were first used during haemofiltration and they showed haemodynamic improvement in septic patients [38]. The main inconvenience of this method is the loss of proteins, albumins in particular. Optimisation of the technical parameters of these membranes and their use in the diffusion method rather than convective method considerably reduces albumin loss [14]. Application of the already available modern filters, containing, e.g. a super-high-flux membrane with optimised cut-off makes it possible to preserve the albumins and purify the blood of cytokines [49].

B. Pharmacological methods

Pharmacological methods make for another strategy for modulating the immune response in sepsis. Any attempts to use hydrocortisone and activated protein C (APC) in sepsis were unsuccessful [33,53]. APC was used due to its anticoagulant properties and beneficial impact on the acute and chronic inflammatory process. It was discontinued since there was no evidence of its clinical efficacy in sepsis and because of the adverse effects in the form of dangerous bleedings. Current trials involve protein engineering and they are carried out with a view to creating a new, more clinically effective and safer APC formula [44].

The recent failure of hydrocortisone and APC were followed by new molecules, which have proven to be beneficial in preliminary studies. These molecules may have a positive impact on immune disorders in the course of sepsis. Their activity pertains to the immune system cell count, phenotype and function.

Interleukin 7 (IL-7)

Interleukin 7 (IL-7) has a basic impact on the survival of lymphocytes and it participates in many functions of leukocytes, which is why it may be considered as an element of adjunctive therapy is sepsis. In the animal peritonitis model, recombinant human IL-7 (rhIL-7) blocked the apoptosis of CD4+ and CD8+ T cells, restored the production of interferon gamma (IFN-γ) and improved the trafficking of leukocytes to the septic focus by increasing the expression of adhesion molecules lymphocyte function-associated antigen-1 (LFA-1) and the very late antigen-4, (VLA-4). The application of rhIL-7 improved the survival rate of animals in the course of sepsis [56]. This ability to improve the immune functions of lymphocytes was confirmed in an *ex vivo* study, which demonstrated that rhIL-7 increased the phosphorylation of signal transducers and activators of transcription-5 (STAT-5) and the induction of B-cell lymphoma 2 (BCL-2) proteins [59].

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

Minor clinical trials involving patients with sepsis and comorbid immunosuppression, defined as reduced monocyte HLA-DR expression, have demonstrated the beneficial impact of GM-CSF on the improvement of HLA-DR expression. In the case of monocytes, also in *ex vivo* conditions, a beneficial impact of GM-CSF on the production of proinflammatory cytokines, induced by the Toll-like receptor 2/4 (TLR 2/4) was also noted. The clinical effect (the duration of mechanical ventilation, organ dysfunction, the time spent in the ICU and the duration of hospitalisation) was better in the group receiving GM-CSF [34].

Interferon gamma (IFN-γ)

Similarly to GM-CSF, IFN-γ may restore the immune functions of leukocytes in septic patients. In healthy volunteers who received LPS intravenously, IFN-γ limited the reduction of TNF release induced by LPS when compared to placebo. IFN-γ also increased the monocyte HLA-DR expression [26]. In studies on a small group of patients, IFN-γ, when additionally used with the standard therapy, improved the treatment results of invasive fungal infections and rebuilt proper function of the immune system [2,11].

PD-1, PD-L1 and CTLA-4 antagonists

Increased expression of the programmed death-1 (PD-1) in the lymphocytes of septic patients may be important in the sepsis-related T cell anergy. Blocking this route was tested on an animal fungal sepsis model. Antagonist antibodies for PD-1 and its ligand PD-L1 restored the expression of IFN-γ and HLA-DR and improved the survival rate of the infected animals [6]. This therapy is already used in cancer treatment, and it will soon be the object of studies on sepsis treatment [4]. In the study referred to above [6], the authors blocked the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) – a molecule with effects similar to PD-1 in the suppression of T cell function. This blockage restored the expression of IFN-γ and HLA-DR improved the survival rate of the infected animals.

Intravenous immunoglobulins (IVIG)

Intravenous immunoglobulins are used to modify the immune response in many immune disorders. Standard or IgM-enriched polyclonal IVIGs may be useful in sepsis treatment as an auxiliary immunomodulatory therapy. The results of the meta-analysis of IVIG application in septic patients published in 2013 were not clear [1].

Practical significance of the presented immunomodulatory treatment methods in sepsis

As has been mentioned above, sepsis should be treated based on valid international guidelines [46]. The proposed immunomodulatory treatment methods presented in this paper, involving both the extracorporeal blood purification and pharmacological methods, are yet

to be added to these guidelines. Many experts believe that once the results of randomised clinical trials are available, the adjunctive immunomodulatory therapies will soon become common in the treatment of sepsis. Extracorporeal blood purification methods are widely used in intensive care and applied in renal replacement treatment in patients with acute renal failure (haemofiltration), in the treatment of autoimmune diseases (plasma exchange) and in the treatment of some cases of acute poisoning (adsorptive membranes). As such, these methods are reimbursable and there will be no problem financing them once they are incorporated into immunomodulatory treatment. If the efficacy of pharmacological methods in immunomodulatory therapy is demonstrated and they are included in current guidelines, they can be financed within the budgets of intensive care units.

However, what is essential for the introduction of immunomodulatory treatment in sepsis is the availability of the methods of diagnosing immune system dysfunctions in daily clinical practice. At present, only the monocyte HLA-DR expression represents a "golden standard" in the identification of patients who may benefit from immunostimulation treatment. The clinical trials currently in progress will make it possible to isolate other biomarkers useful in daily clinical practice [36]. Such diagnostics will make it possible to individualise the immunomodulatory treatment and adapt it to the current condition of the immunological system of a septic patient, i.e. to either suppress the excessive inflammatory response using extracorporeal blood purification or fight immunosuppression using pharmacological immunostimulant methods.

Conclusion

Despite the considerable recent advancement in the treatment of sepsis, the mortality rate in the course of sepsis is still high. Aside from the conventional treatment methods used for over a decade now, the immune disorders accompanying sepsis have been gaining increased interest. They have a significant impact on the clinical course of sepsis, contributing to its morbidity and mortality rate. Studies to date on small groups of septic patients have shown that, e.g. immunostimulants are able to rebuild the immune functions with a good clinical effect. So diagnosing the immune disorders accompanying sepsis may help apply targeted immunomodulatory therapy and thus offers a better prognosis. The basic problem in implementing such treatment is defining the right biomarkers and laboratory methods permitting "bedside" diagnosis of the immune system dysfunctions. FCM gives high hopes in this respect. The basic assumption underlying the immunomodulatory therapy is limitation of the negative effects of the immune response in sepsis. The potential suggested treatment methods include both the techniques of extracorporeal blood purification and pharmacological methods. Some of them are very interesting and have a chance at being included in clinical practice in the nearest future.

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