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Current Problems of the Diagnostics and Treatment of Sepsis and Burn Injuries: The Modified Pathogenetic Concept

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Abstract

Background: The deep understanding of pathogenesis is a key moment in the formation of the modern strategy of modern medicine. We conducted the thorough analysis of the microscopic processes occurring in the bodies of patients with purulent-septic complications. The modified pathogenetic concept of the diagnostic and treatment model of diseases with septic complications is presented. The obtained information about the mechanisms of origin and development of these diseases is fundamentally important for finding the modern effective methods of treating patients. The aim of the research is to modify treatment tactics for patients with sepsis and burn injuries based on the modified pathogenetic concept using modern diagnostics, *i.e.* the method of fluorescence spectroscopy (MFS) and biomarkers. Materials and Methods: The proposed modified pathogenetic concept of the diagnostic and treatment model of diseases with purulent-septic complications along with standard methods was used successfully for effective treatment of 15 patients with sepsis and 25 with burn injuries. Results: 3 main scenarios of behaviour of spectral-fluorescence characteristics of patients with sepsis are illustrated. Spectral-fluorescence markers of sepsis were studied, which are informative 24 to 48 hours before the appearance of obvious clinical and laboratory signs of significant changes in the general somatic status of patients. Conclusions: The proposed diagnostic and therapeutic approach is new and fundamentally important for diagnostics and monitoring of the process of treatment of patients with purulent-septic diseases and burn injuries. An in-depth understanding of the dynamics of septic complications and the corresponding changes of the main markers of these diseases during treatment is especially relevant. The use of infusion therapy with solutions of donor albumin as an effective pathogenetic treatment is scientifically justified.

Keywords

Purulent-Inflammatory Diseases, Sepsis, Modified Pathogenetic Diagnostic and Treatment Model, Method of Fluorescent Spectroscopy, Biomarkers, Albumin Infusion

1. Introduction

For more than thirty years, special attention has been paid to the diagnosis and treatment of sepsis. The international protocol for its intensive therapy was updated periodically with the participation of dozens of leading organizations, well-known scientists and experts [1]. Unsatisfactory results of treating sepsis were related directly to the lack of the effective methods of its express diagnosis, especially early [1] [2] [3]. When treating patients with severe pathology, insufficient attention was mostly paid to the microscopic processes that occur in the patients' bodies, and especially in their blood. Thus, it did not always lead to the discussion from the first principles and the significant improvement of traditional treatment schemes. In particular, when conducting biochemical blood analysis with determination of protein fractions and albumin level, it was impossible to detect the real changes in the structure of albumin molecules in septic complications. In this regard, it was fundamentally important to develop the pathogenetic concept for the significant improvement of diagnostic tactics, especially at the early stage of the development of purulent-inflammatory diseases and sepsis. The particular attention should be focused on the problems of diagnosis, treatment tactics and the effective monitoring of the condition of patients and correction of the treatment process.

2. Literature Review

Cytokines (interleukins: IL-1, IL-6, IL-8, IL-10, IL-12), presepsin, factor platelet activation (PAF), transforming growth factor-β (TGF-β), C-reactive protein (CRP), lactate and procalcitonin (PCT) are the sensitive biomarkers of endotoxicosis and systemic inflammatory reaction in the severe condition [2]. The considerable attention was paid to their research. We will dwell briefly on the most important information about these biomarkers and discuss the problem of their use for the diagnosis of purulent-septic complications in the medical practice. We shall make the extensive use of the information presented in the papers [1] [2] [3] [4].

The primary model of sepsis is the immune response to endotoxin, LPS, which was found in the cell walls of gram-negative bacteria. LPS is an excellent example of the pathogen-associated molecular pattern (PAMP) [3]. Innate immune cells, such as macrophages, have receptors that recognize different types of PAMPs. When interacting with bacterial ligands, these receptors stimulate macrophages to produce TNF-α, IL-1β та IL-6. These pro-inflammatory cytokines

cause the systemic inflammatory response characteristic of early sepsis. For many years doctors believed that sepsis was an overreaction of the innate immune system to a bacterial infection. The 1991 consensus conference defined "sepsis" as the combination of infection with two or more signs of SIRS.

Roger C. Bone is now believed to have recognized that sepsis is more than severe hyperinflammatory SIRS [5]. The importance of CARS (compensatory anti-inflammatory response syndrome), which often follows a hyperinflammatory phase, has also been highlighted, especially in patients who develop sepsis [6]. In patients with sepsis, there are also signs of severe organ dysfunction. This can include lung, liver and/or kidney damage, as well as the cognitive impairment. The terminal stage of sepsis is septic shock, in which patients develop cardiovascular collapse and are unresponsive to infusion and vasopressor therapy. In the dynamics of the course of sepsis, two phases should be distinguished. With the development of SIRS, the hyperinflammatory phase occurs at first. Pro-inflammatory and anti-inflammatory cytokines are produced in the body at the same time, but when their imbalance is disturbed, signs of CARS with immunosuppression and multiple organ dysfunction appear. At this stage, it is fundamentally important to carry out the effective treatment before the development of irreversible processes.

As the sepsis paradigm has evolved over time, various approaches to its diagnosis and treatment have been tested, including various biomarkers. The main focus, starting in 1980, was directed on the early phase with hyperergic inflammatory response, for which high doses of corticosteroids were used, which were considered an important component of its treatment. The subsequent research and advances in the treatment of major sepsis problems have been closely linked to the use of pro-inflammatory cytokines, particularly TNF-α, IL-1β and IL-6, which cause SIRS [3]. At the same time, CRP also appears, the synthesis of which is activated in the liver with the help of IL-6, as well as PCT. CRP and PCT have become new potential biomarkers since 2003.

At the end of the last decade, lactate was used as a biomarker for the diagnosis and treatment of septic complications. Later, when the therapy was aimed at the anti-inflammatory phase of sepsis, the new scientific research continued and new biomarkers were studied successfully. After recognizing the importance of CARS, biomarkers of the immunosuppressive phase of sepsis deserve considerable attention. There is the sufficient convincing evidence that adaptive immunity is impaired in patients with severe sepsis. The earliest sign of weakening of the immune response both in patients with sepsis and in people after trauma is the decrease in the expression of proteins of the major histocompatibility complex (MHC) class II (HLA-DR) - human leukocyte antigen on the surface of macrophages and other antigen-representing cells.

The clinical studies have focused on monocyte HLA-DR expression, which was markedly suppressed in most patients with sepsis initially, but recovered within ten days in surviving patients [7]. Similar depression may occur after severe trauma, and failure to recover within the first week of hospital stay in sur-

viving patients is a real predictor of developing sepsis in these patients. The low levels of HLA-DR expression predict, accordingly, a low percentage of patient survival, as well as an increased risk of nosocomial infection. The clinical utility of measuring IL-10, which inhibits the expression of MHC class II, and TGF-β, which suppresses the proliferation of T cells, has been proven. The elevated levels of IL-10 predict the mortality of patients with severe sepsis. It has also been disclosed that they correlate with inhibition of HLA-DR monocyte expression. IL-10 is a reliable biomarker of neonatal sepsis [8]. In addition, it was also shown that at early and late onset of sepsis, rather a rapid increase in the level of IL-10 was practically not noticed. TGF-β has been shown to promote tissue repair, but its role is not as important as that of IL-10.

None of the biomarkers discussed in the above publications are perfect, but in principle they can be useful. In order to study the possible change in the health status of patients during treatment more deeply and to direct this process in the right direction, it would be very important to know the dynamic picture of changes of biomarkers and to understand which of them reflect most globally and affect the change in the health status of patients. Over time, much attention is paid to the search for new biomarkers of septic complications in the field from SIRS to CARS.

3. Data and Methodology

3.1. Data Source

When conducting the biochemical blood analysis with determination of protein fractions and albumin level, it was impossible to detect the real changes in its structure during septic complications. In this regard, it was fundamentally important to develop the pathogenetic concept in order to improve the diagnostic tactics significantly for patients with purulent-septic diseases.

Modern clinical studies of the level of HSA have proven its important diagnostic value for assessing the condition of patients and predicting the course of their diseases [9]. The basis for this is the ability of albumin to form complexes with the products of bacterial life - toxins, which provide its detoxification function and are important for detecting of pathologies. The reverse side of the sorption of toxins by albumins is inhibition of the transport function of proteins. It has been established that the release of toxins from the local pathological focus leads to the syndrome of endogenous intoxication (EI). The body's protection against toxic compounds is carried out by the immune system, but it ensures the elimination of only high-molecular foreign substances with a molecular weight of at least 5000 Da. The elimination of low molecular weight toxins is provided by blood transport proteins.

3.2. Research Results

3.2.1. The Modified Diagnostic and Treatment Model of Purulent-Inflammatory Diseases and Sepsis

Over the past twenty years, some authors [10] [11] have demonstrated the diag-

nostic value of MFS, which was illustrated specifically on the disease models "in vitro" [12], as well as specifically "*in vivo*" and confirmed in clinical practice for patients with obstetric [13] and surgical [14] pathologies and with burn injury [15] [16]. Considerable attention was paid to the understanding of the essence of the pathological processes that occur in the bodies of patients with purulent-septic diseases at the molecular level. It is based on the fact that in diseases accompanied by EI, part of the albumin molecules are blocked by toxins. As a result, there are two types of albumin molecules in their blood: normal and blocked by toxins. At the same time, pathological molecules lose their ability to perform their main functions, namely transport and detoxification. So, the pathogenetic concept of the diagnostic and treatment model of purulent-inflammatory diseases and sepsis was proposed [12]. Since part of the albumin molecules in the blood of patients are blocked by toxins, there are two types of albumin molecules in their blood: normal concentration (X) and blocked (concentration (1-X)). Blocked albumin molecules lose their ability to perform their main functions, namely transport and detoxification. This allows us to understand better the processes of genesis during the course of sepsis in patients' bodies.

Taking into account the above-discussed features of the protection of patients with purulent-septic diseases from toxic compounds, the modified concept of the diagnostic and therapeutic approach of purulent-inflammatory diseases and sepsis is proposed. The proposed concept consists in determining X^o—the limit minimum concentration of normal albumin in the blood of the patient with sepsis. In the case of $X > X^o$, albumin molecules eliminate successfully toxins. The problem of sepsis is complex, and its solution must be comprehensive. The diagnosis and control of the process of its treatment can also be carried out within the framework of MFS and with the use of biomarkers. The most important role of biomarkers is to obtain information about X^o (SIRS). As a result, we can get information about I_F and λ_{max} of precisely at the time of SIRS. At the same time, the approach proposed by us within the framework of the MFS will continue to be relevant. It will allow us to study the BS samples of patients and analyze changes in dynamics of I_F and λ_{max} in details. In the future, it is necessary to measure the dynamics of IL-6 and other biomarkers that appear when the patient's condition worsens (after the transition to the CARS state). At the same time, there is a change of I_F and λ_{max} in this state, information about which we will receive within the framework of the MFS. But I_F and λ_{max} can also provide the information about how they are affected by donor albumin infusions. We shall see that donor albumin infusions will also reduce biomarkers that appear when a patient's condition deteriorates (for example, IL-6 if albumin infusions are used in treatment after biomarkers appear). The fundamental role in the diagnostic approach has the information obtained within the MFS regarding I_F and λ_{max}, but we do not know how they behave in SIRS, and even more so between SIRS and CARS, because no one has done this.

3.2.2. Study of Spectral-Fluorescent Characteristics of BS of Patients with Sepsis

Now consider, for example, the results of the examination within the framework of the MFS of several patients with sepsis and with burn injuries.

Figure 1, Table 1 present the results of the study of spectral-fluorescence characteristics of two patients with sepsis. Both of them had sepsis-epiduritis. The first patient was young (33 years old), she had no concomitant diseases, but there was a late application for medical help. The second patient was older (60 years old), but he addressed timely for medical help. Bacteremia was diagnosed in both patients. A thorough clinical and laboratory examination was conducted for them. Antibiotic and infusion therapy in significant volumes were prescribed. Patient 1 was admitted to the hospital due to the manifestation of a septic condition. MFS helped to identify the septic peak in the long-wave region (Figure 1, curve 1) and to decide the further rational choice of treatment tactics. Further studies of the FS of BS of this patient (Figure 1, curves 3, 4) proved that bacteremia was not overcome completely in her body, although the long-wave septic peak disappeared. However, the competitive struggle between bacteremia and compensatory capabilities of the patient's body in combination with complex medical measures continued. Only the subsequent long treatment process of this patient led to the final suppression of endotoxemia and recovery of this patient (Figure 1, curve 5). Curve 1 is very interesting from the point of view of

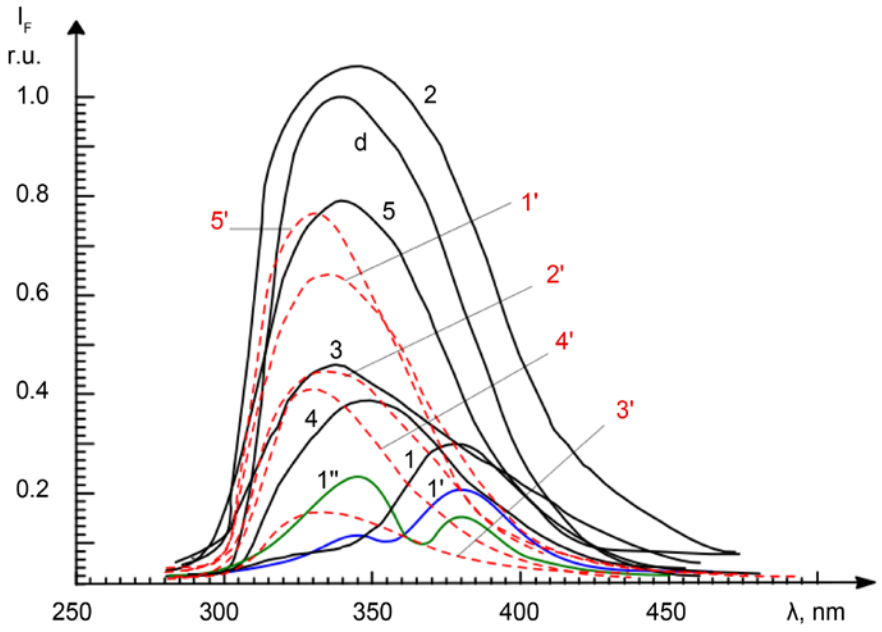

Figure 1. Fluorescence spectra of the blood serum of a person with sepsis-epiduritis who was treated in Emergency hospital in 2001-2002: 1—28.12.2001; 1'—30.12., 1"—02.01.2002; 2—04.01.2002; 3—12.02.2002 p.; 4—19.03.2002 p.; 5—04.06.2002 p. and a patient with sepsis-epiduritis, who was treated in 2002 in Emergency hospital: 1'—03.06; 2'—05.06; 3'—06.06; 4'—07.06; 5'—10.06 and blood serum of the donor (d). λex = 280 nm, donor blood serum (d). λex = 250 nm (340 nm—"normal peak", 380 nm—"septic peak").

Table 1. Changes of the spectral-fluorescence characteristics of the blood serum of two patients with sepsis-epiduritis.

N	d	1	1'	1'	1"	1"	2	3	4	5	1'	2'	3'	4'	5'
Date	28.12	28.12	30.12	30.12	02.01	02.01	04.01	12.02	19.03	04.06	03.06	05.06	06.06	07.06	10.06
λ_{max}, nm	340	380	380	345	380	345	345	337	349	340	336	334	333	330	331
I_F, r.u.	1.0	0.3	0.21	0.12	0.15	0.23	1.07	0.46	0.39	0.79	0.64	0.44	0.16	0.41	0.76

the ideology of biomarkers. The main contribution to FS here is given by blocked albumin molecules, and a minor contribution at λ = 345 nm indicated that she was in the CARS state. This confirms that in this condition, even a small amount of normal albumin molecules ensured the survival of this patient in the severe septic condition.

In the case of the second patient (**Figure 1**, dashed curves), the source of infection in his body was removed surgically at the beginning of the treatment process. The detailed monitoring of the treatment process within the framework of the MFS showed that the behaviour of the fluorescence curves during the recovery of this patient was qualitatively consistent with the behaviour of the recovery of the previous patient. Unfortunately, during the treatment of the above-mentioned patients, whose monitoring was followed within the framework of MFS, no pathogenetic concept was proposed, and infusion of donor albumin solutions was not used. However, both patients recovered and were discharged successfully from the hospital.

The third scenario studied by us within the framework of the MFS demonstrates clearly the behaviour of the FS of BS of the patient with sepsis caused by multiple soft tissue foci of infection on the basis of diabetes (**Figure 2(a)**, **Table 2**). This person was admitted to the hospital at the beginning of the formation of the septic state in her body. So, no two-peak structure was detected during the study of the FS of her BS. After the surgical intervention, against the background of intensive antibacterial and anti-inflammatory therapy, there was a gradual decrease in the fluorescence intensity of her BS, but the patient's condition did not change practically for three days. Unfortunately, this scenario was not so optimistic. According to the pathogenetic concept, in this case, complete albumin molecules were also blocked by sugar residues.

In this case, there were actually two types of pathological albumin molecules: blocked by toxins and an increased number of glycolyzed ones. This patient's condition worsened suddenly within one day against the background of intensive antibiotic therapy, which can be explained by the presence of a number of serious concomitant diseases and her advanced age. Glycolization of albumin molecules also contributed to this, due to the presence of diabetes in the patient. The patient died as a result of generalization of the infection and multiple organ failure.

However, despite such a difficult scenario of the course of the disease, presented in **Figure 2(a)**, MFS gives us the opportunity to discuss theoretically

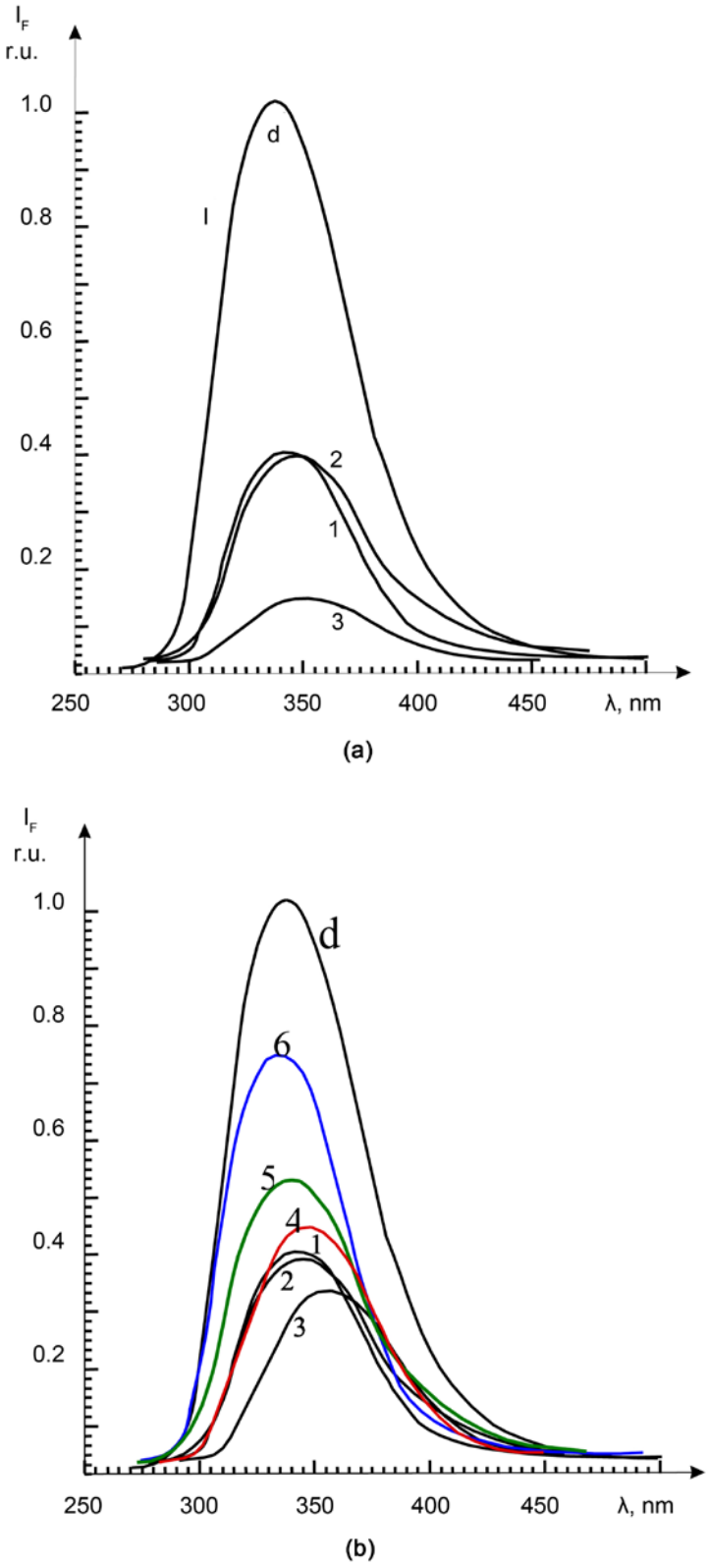

Figure 2. (a) Fluorescence spectra of blood serum of the patient with sepsis and diabetes, who was treated in 2002 in Emergency hospital and blood serum of a donor (d). λ_{ex} = 280 nm. (b) Fluorescence spectra of blood serum of the patient with sepsis and diabetes, who was treated in 2002 at Emergency hospital and blood serum of a donor (d). λ_{ex} = 280 nm.

Table 2. (a) Changes in the spectral-fluorescence characteristics of the blood serum of person 3, a patient with sepsis and diabetes. (b) Changes in the spectral-fluorescence characteristics of the blood serum of person 3, a patient with sepsis and diabetes.

(a)

N	d	1	2	3
Date	03.06	03.06	05.06	06.06
λ_{max}, nm	338	342	347	351
I_F, r.u.	1.0	0.41	0.40	0.15

(b)

N	d	1	2	3	4	5	6
Date	03.06	03.06	05.06	07.06	09.06	11.06	14.06
λ_{max}, nm	338	342	347	355	345	338	334
I_F, r.u.	1.0	0.41	0.40	0.33	0.45	0.53	0.75

another possible scenario for the treatment of this patient, starting from 03.06, which, unfortunately, was not implemented. It could have been implemented if the pathogenetic concept of the development of purulent-inflammatory diseases and sepsis had been proposed at that time. According to this scenario, the patient should be injected with 150 - 200 ml of 20% donor albumin and continue to monitor within the framework of the MFS FS of BS and perform albumin infusions after 2 - 3 days until complete recovery. The scenario of such a possible variant of the treatment process for this patient is presented in **Figure 2(a)** and in **Table 2(b)**.

At the same time, it would be necessary to adjust the tactics of diabetes treatment as well. Although this did not give a full guarantee of the recovery of this patient, the mentioned procedure should be performed, giving the patient the last chance to survive. It is obvious that these results could be obtained only within the framework of MFS. The final result of treatment also depends on the presence of concomitant diseases that require the additional treatment. The actual treatment of this patient should be carried out immediately according to a different scenario, using infusions of donor albumin and adjusting the treatment of diabetes.

The particular attention should be paid to the relevance of this problem for high-income countries due to the increase of the number of people, including pregnant women, with obesity and diabetes, which contributes to the increased risk of developing of purulent-septic complications. Obesity can affect negatively a woman's health, causing insulin resistance, dyslipidemia, hormonal and psychological problems, along with sexual problems during menopause [17]. About 6% of albumin molecules in BS of healthy donors are glycosylated. At the same time, 9% - 12% of patients with diabetes are in a glycosylated state due to the presence of hyperglycemia [12]. So, the sum of pathological and glycosylated albumin molecules should be considered pathological. Glycated hemoglobin

(HbA1c) is an early prognostic marker for the diagnosis of diabetes, which enables us to detect this disease at the early stages, and also allows us to prescribe the appropriate treatment in order to prevent its development. Normally, this indicator is 4% - 5.6%. A level of A1c (HbA1c) between 5.7% - 6.4% means that a person has prediabetes. As a result, her chances of developing diabetes are high. The closer the HbA1c level is to 6.4%, the higher the risk of developing diabetes. An indicator of 6.5% and above indicates that a person already has diabetes. In 1977, it was proposed to determine HbA1c, which is a stable connection of hemoglobin with glucose, formed as a result of non-enzymatic glycosylation of hemoglobin for the assessment of glycemia. The use of HbA1c for the diagnosis of the diabetes has been approved by the WHO since 2011. According to the recent data, it is believed that HbA1c underestimates glycemic control in patients with diabetes. At the same time, glycosylated albumin is a more reliable indicator of glycemic control. The role of HbA1c in patients with chronic renal failure requires further research. Logically, patients with diabetes are prone to the occurrence of purulent-septic complications in the body and their long course. The logical hypothesis is that "albumin overloaded with sugar residues" is not able to bind completely and eliminate toxic products from the body, which leads to the deepening of endogenous intoxication. Pregnant women with diabetes are a risk group for the formation of postpartum purulent-inflammatory diseases. If the medical institution does not have the possibility to monitor the treatment process within the framework of MFS, it is necessary to carry out the detailed monitoring of the state of health of patients, in particular, to carry out clear monitoring of the level of glycemia in the BS. When the level of glycemia increases, it is advisable to correct the therapeutic tactics of diabetes and use infusions of a 20% solution of donor albumin.

The dynamics of changes of the spectral-fluorescence characteristics of the BS of patients with sepsis reflects objectively the clinical features of the course of this disease, which depends significantly on the quality of diagnosis and correlates with the effectiveness of treatment tactics.

3.2.3. The Study of Spectral-Fluorescent Characteristics of BS of Patient with Burn Injury

Figure 3(a) presents the results of research in the dynamics of FS, and in **Table 3(b)**—data for spectral-fluorescence characteristics of the patient with a burn injury (28% burn surface area), who obtained the inpatient treatment at St. Luke Hospital in February 2017. He was prescribed immediately the appropriate treatment, including the antibiotic therapy and infusion therapy with a volume of up to 3 litres daily, as well as infusions of 10% donor albumin (06.02, 10.02 100 ml each day). The condition of this patient was serious. Despite the intensive treatment, his condition deteriorated significantly during the first 5 days. This is evidenced by a decrease in fluorescence intensity (Curves 1, 2). He had a fairly significant EI. Thus, the treatment process was corrected, including additional infusions of a 10% solution of donor albumin (February 15, 18, 26, and March 2,

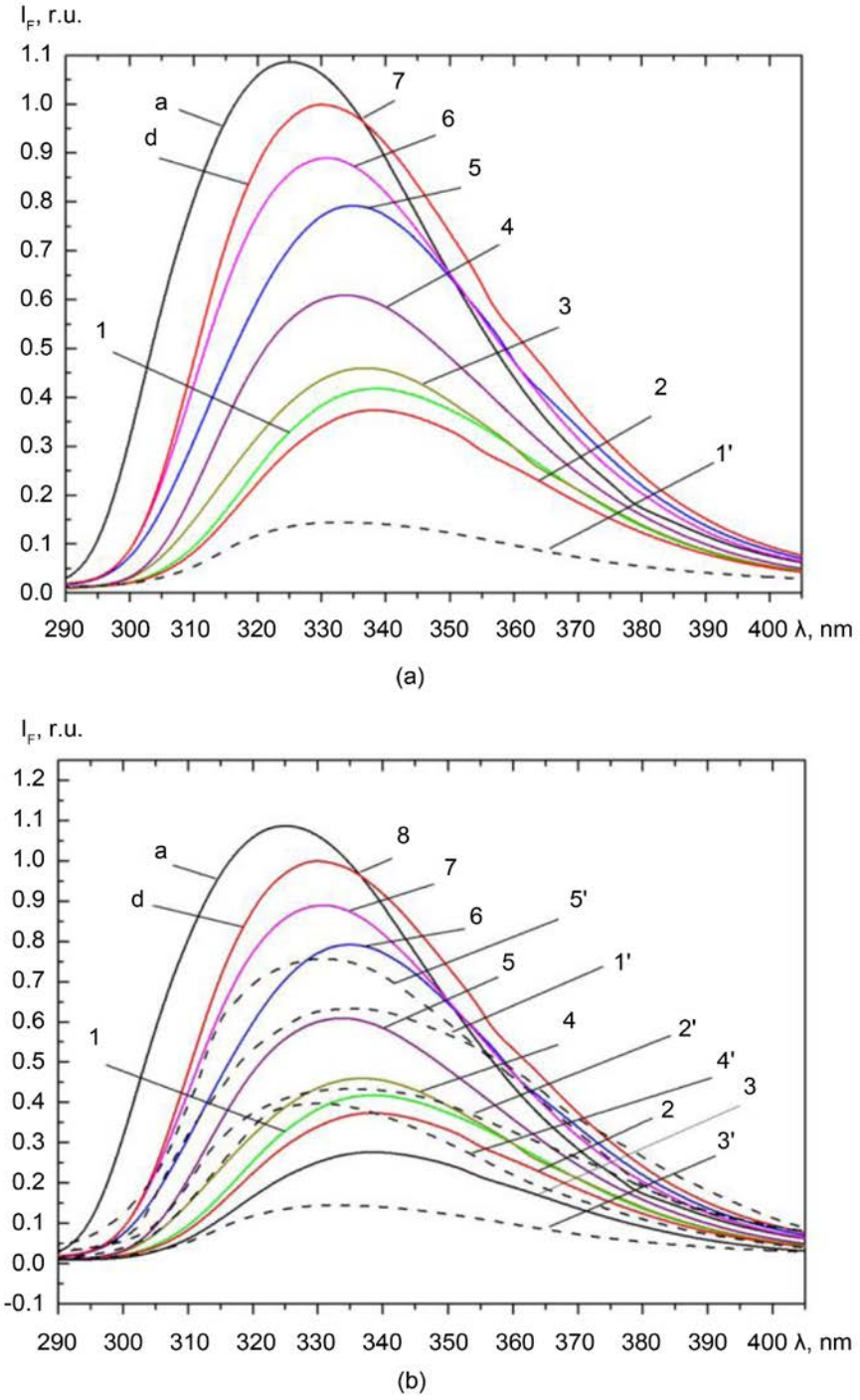

Figure 3. (a) Fluorescence spectra of the blood serum of the patient with a burn injury who was hospitalized in 2017 in the dynamics of treatment, a patient with sepsis (1') who was treated in 2002, a donor (d) and a 20% solution albumin (a). λ_{ex} = 280 nm. (b) FS of BS of the patient with a burn injury who was hospitalized in 2017 in dynamics during treatment, a patient with sepsis (1'-5') who was treated in 2002, a donor (d) and 20% donor albumin (a). λ_{ex} = 280 nm.

100 - 150 ml each day). These infusions made it possible to improve significantly the functioning of the body's detoxification systems with the gradual normalization

Table 3. Changes in the spectral-fluorescence characteristics of the blood serum of the patient with a burn injury. (b) Changes in the spectral-fluorescence characteristics of the blood serum of the patient with a burn injury.

(a)

N	A	D	1'	1	2	3	4	5	6	7
Date	06.06	06.06	06.06	9.02	14.02	22.02	27.02	03.03	10.03	31.03
λ_{max} nm	330.1	333.1	333	335.1	339.1	337	334	335.1	331.1	332.0
I_F, r.u.	1	1	0.16	0.41	0.37	0.46	0.61	0.79	0.89	0.95

(b)

№	1	2	3	4	5	6	7	8	1'	2'	3'	4'
Date	9.02	14.02	22.02	25.02	28.02	03.03	10.03	31.03	3.06	5.06	6.06	7.06
λ_{max} nm	335.1	339.1	337	337	334	335.1	331.1	332.0	335.2	335.2	334.1	331.6
I_F, r.u.	0.41	0.37	0.27	0.46	0.61	0.79	0.89	0.95	0.63	0.43	0.14	0.40

of endogenous albumin synthesis by the liver. As a result, the fluorescence intensity of the BS of the patient increased markedly, and the long-wavelength shift of FS leveled off (Curves 3 - 7). After that, the patient was discharged from the hospital in the satisfactory condition.

Figure 3(a) (Curve 2) and **Table 3(a)** demonstrate a decrease in the fluorescence intensity of FS. If we do not take this fact into account and do not prescribe an infusion of donor albumin, there will be an increase in EI and we will get curve 3 within the framework of MFS 22.02 (see **Figure 3(b)**). It can be seen from this figure that the patient's condition has approached septic (Curves 3 and 3' are close to each other). Thanks to the monitoring of the treatment process within the framework of the MFS, it was possible to identify a threatening situation for this patient. He should be given several sessions of infusion therapy with a solution of donor albumin until the possible improvement of his health and his recovery. The scenario of his treatment at the final stage took place under the supervision of the MFS and is illustrated in **Figure 3(b)** and **Table 3(b)**. If the infusion of donor albumin had not been prescribed on 22.02, his health could have deteriorated significantly. In this case, treatment should be continued using infusion therapy with a solution of donor albumin, although there was no absolute guarantee of successful completion of the treatment process in this case. It is fundamentally important to be able to monitor the treatment process within the framework of the MFS. At the same time, it is very important to carry out the detailed monitoring of the patient's condition during the treatment process, adjusting the treatment process if possible. Summarizing, we note that the dynamics of changes in the spectral-fluorescence characteristics of patients with sepsis and burn injury during the treatment reflects properly the clinical features of the

course of these diseases.

4. Conclusions

1) The method of diagnostics of purulent-inflammatory diseases and sepsis was proposed within the framework of the MFS.

2) It has been established that the structure of FS of BS in the patients with these diseases is an effective marker of its severity.

3) At the same time, in patients with severe sepsis, the structure of FS of BS is double-peaked, which reflects the presence of two types of albumin molecules in the blood of patients.

4) Spectral-fluorescence characteristics obtained within the framework of MFS have a pre-manifest nature. These changes are usually registered 24 - 48 hours before the appearance of obvious clinical and laboratory signs of the patients' condition.

5) The modified pathogenetic concept of the diagnostic and therapeutic approach to purulent-inflammatory diseases and sepsis is proposed and presented.

6) A modern approach for diagnosis and effective control of the treatment process within the framework of MFS and biomarkers using infusions of donor albumin solutions was proposed.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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