

The Pathogenetic Concept of the Diagnostic-Treatment Approach for Patients with Purulent-Septic Complications

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Abstract

Background: The significant improvement of immediate and long-term functional results of treating patients is the fundamental problem of modern medical science. A deep understanding of the pathogenesis is the key point in creating the management strategy for patients with various diseases. Information about the mechanisms of origin and development of purulent-inflammatory diseases and sepsis is essential for finding effective ways to prevent and treat them. **The aim of the research** is to use the method of fluorescence spectroscopy in creating the pathogenetic diagnostic and treatment model for the prevention and treatment of purulent-inflammatory diseases and sepsis, modification of treatment tactics, search for new markers of purulent-septic diseases, as well as monitoring of patients during the treatment. **Materials and methods:** The proposed approach, along with standard diagnostic methods, was used to organize the treatment process of 100 patients with purulent-inflammatory diseases, including 15 patients with sepsis, 35 with acute inflammatory abdominal pathology, 20 patients with burn injury (main group) and 35 patients with burn injury (comparison group). **Results:** The behavior of spectral-fluorescent characteristics in their dynamics has been studied, and the new markers for assessing patients' conditions have been proposed. Their effectiveness for the diagnosis of purulent-septic diseases has been proved, which advances the results of standard research methods by 24 - 48 hours. **Conclusions:** The proposed diagnostic and treatment approach is fundamentally important for diagnosis and monitoring during the treatment of patients with purulent-septic diseases. Particularly relevant is the proposal to modify the treatment process for these patients, associated with the use of infusion of donor albumin solutions.

Keywords

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

1. Introduction

Over the last thirty years, much attention has been paid to the diagnosis and treatment of sepsis. Significant efforts of researchers were focused on the specific features, clinical characteristics and nature of the disease. At the same time, insufficient attention was paid to the pathogenetic assessment of the occurrence and development of purulent-septic complications. The issues of sepsis diagnosis, especially its monitoring and treatment, have not been resolved adequately. They require detailed justification as well as the quick and adequate solution by using modern scientific approaches. Particular attention should be paid to the problem of optimizing the treatment tactics and the effective monitoring of patients during the treatment. Significant efforts in this research within the proposed pathogenetic concept will be focused on the study of blood serum (BS) of surgical patients and patients with burn injury.

2. Literature Review

According to the WHO, sepsis is the dangerous dysfunction of the internal organs caused by dysregulation of the body's response to infection. Three conciliation conferences on the problem of sepsis have been held (1991, 2001, 2016) in order to discuss new strategies to solve it. Over this time, the definition of sepsis and septic shock has changed three times; periodically the international intensive care protocol was updated with the participation of dozens of leading organizations and experts [1].

In May 2017, the 70th session of the World Health Assembly adopted a resolution on sepsis. According to it, the primary attention should be focused on improving early diagnosis, finding new markers and improving treatment tactics and monitoring of patients. The changes in the definition of sepsis over the past 30 years and the main approaches to solving this problem are described in detail in the research [2]. Sepsis occurs when the body's response to the infection causes damage to its own tissues and organs and can cause the significant deterioration of the patient's condition and even his death. It is estimated to affect more than 30 million people each year and can kill 6 million people [3]. This problem is quite typical for low- and middle-income countries. According to the WHO, sepsis occurs annually in 3 million newborns and 1.2 million of children [4]. One of ten maternity deaths is due to obstetric sepsis. 95% of maternal sepsis deaths occur in low- and middle-income countries [5]. Thus, this is a global problem that requires the adoption of the effective strategy to solve it.

At the same time, since 2001, at the suggestion of Professor I. Herych (Lviv,

Ukraine), a series of studies of BS of patients with purulent-inflammatory diseases and sepsis was started within the method of fluorescence spectroscopy (MFS) [6] [7] [8] [9]. It is the most universal method in biological spectroscopy.

MFS is now successfully used in the medical practice for conducting up-to-date prospective studies based on the latest developments in molecular biology. They allow identifying certain genetic mutations in humans and their individual predisposition to the development of certain pathological conditions. The results of these studies open the way to the successful development of “personalized medicine”. It means that it is possible to identify the individual risk of certain diseases for each individual and appropriate measures to prevent the possibility of their occurrence and progression. This opens vast opportunities for finding effective drugs, the so-called “gene therapy”, which offers broad prospects for the treatment of various diseases, including cancer.

The method of fluorescence spectroscopy is successfully used for diagnosis in oncohematology to detect genetic mutations that cause an increased susceptibility of the human body to myeloproliferative disease [10], for the diagnosis of polycythemia and other myeloproliferative diseases, including in the dynamics [11], the study of acute lymphoblastic leukemia in children, chronic myeloid leukemia, acute promyelocytic leukemia [12], for the acute myeloid leukemia [13]. If there is a genetic mutation, the course of cancer is more aggressive. This method has also been well established for detecting genetic mutations in prothrombin and Leiden coagulation factor V, which cause an increased susceptibility of the human body to venous thrombosis, which is one of the most common vascular diseases [14].

In the framework of this research, MFS provides the study of the spectral-fluorescent characteristics of BS of patients with pyo-inflammatory diseases and sepsis, when excited BS by light with a wavelength of 280 nm. The choice of this wavelength is associated with the excitation in this area of human serum albumin molecules, which undergo conformational changes in patients with purulent-inflammatory diseases. After the preliminary study and the interpretation of the results in patients with sepsis, the study of the fluorescence spectra (FS) of BS of women with postpartum purulent-inflammatory diseases was conducted in order to prevent the occurrence of obstetric sepsis [15] [16] [17] [18]. The next step was to study the FS of BS of patients with burn trauma, which are model objects for studying the spectral-fluorescent characteristics of patients with sepsis [19]. Understanding the pathogenesis of sepsis is the key point in finding effective ways to prevent and treat it. It develops when the body's response to infection leads to damage to its own organs and tissues and can lead to significant deterioration in health and even death of the patient [20] [21].

The aim of our research is directed at performing the basic tasks of the WHO and applying a pathogenetic diagnostic and treatment model within the MFS for the diagnosis, treatment and prevention of purulent-inflammatory diseases and sepsis.

3. Data and Methodology

3.1. Data Source

The study of the BS of 100 patients with inflammatory abdominal pathology and sepsis who during 2001-2008 were treated in the purulent-septic center of Ambulance Hospital in Lviv were done. Among them, 42 (42%) were patients with aseptic pathology, 43 (43%) patients with preseptic pathology and 15 (15%) patients with sepsis. The BS of 20 patients with burns were examined during 2015-2019. They were treated at the Centre for Thermal Trauma and Plastic Surgery of 8th Clinical Hospital of Lviv. The comparison group consisted of 35 patients with severe burn injuries. The control group included 40 healthy individuals aged 21 to 55 years, with a mean age of 36 ± 1.24 years. The luminescent laboratory of the department of experimental physics at the Ivan Franko National University of Lviv provided experimental data.

Research methods: general clinical, laboratory (general blood and urine tests, biochemical blood test), instrumental examinations (electrocardiogram, X-ray, ultrasound examinations, if necessary, computed tomography (CT) or magnetic resonance imaging (MRI). In addition to standard research methods, the BS of all patients were also examined by the MFS on admission to the hospital and in the dynamics during the treatment. The measurements were performed using the aperture monochromators MDR-2 and MDR-12.

The source of excitation was the deuterium lamp DDS-400. The objects of the study were samples of BS of patients of the main and control groups. Excitation of the BS was carried out at a wavelength of 280 nm, which corresponds to the glow region of human serum albumin. Based on the obtained results for the spectral-fluorescent characteristics of their BS, possible mechanisms of sepsis occurrence and prognosis regarding its prevalence and methods of treatment are proposed and discussed. The main studied indicators were the fluorescence intensity (I_f) and the presence of a change in the position of the SF maxima (λ_{\max}). The characteristic long-wave shift and the corresponding septic peak which can be found only within MFS are revealed.

3.2. Research Results

3.2.1. Pathogenetic Concept of Diagnostic and Treatment Model of Purulent-Inflammatory Diseases and Sepsis

The tactics of previous studies about sepsis were directed to the detailed external assessment of the visual state of the body. Therefore, traditional schemes were used in the treatment. At the same time, insufficient attention was paid to the microscopic processes occurring in the body of patients, in particular in the blood of patients with sepsis. Thus, this did not lead to the improvement of traditional treatment regimens. Even when conducting the biochemical analysis of blood to determine protein fractions and albumin levels, it was impossible to detect real changes in its structure in patients with purulent-septic complications. Therefore, to clarify these changes at the molecular level, it was expedient

to analyze in detail the changes in the structure of the BS in patients with these diseases. So, it was necessary to develop a new pathogenetic concept for sepsis.

Albumin molecules constantly perform transport and detoxification functions in the human body. At the same time, due to changes in the conformation of its molecule, albumin interacts with hydrophobic molecules of endotoxins, absorbs them and promotes excretion from the body. In the presence of endogenous intoxication in the body of patients with purulent-inflammatory diseases and sepsis, the interaction of albumin molecules with the products of bacterial metabolism due to the ability of albumin molecules to complex takes place. The total number of albumin molecules remains constant. At the same time, the number of complete albumin molecules in the serum samples decreases [2]. This leads to the disruption of the patient's body and requires timely implementation of effective treatment measures. However, in previous studies, the above was not taken into account, and it was not definitively clarified what this leads to. In this case, the system of albumin molecules is actually transformed into a disordered system. This requires finding possible ways to preserve the vital functions of the organism in such pathological conditions. The pathogenesis of this phenomenon has not been analyzed in our previous research [2] [6] [7] [8] [9]. Only a deep understanding of the above processes has led to the creation of the pathogenetic concept and the unconventional decision: if the complete albumin when approaching the septic state becomes less and less, so it is advisable to conduct exogenous infusions of albumin in order to replenish reserves of the body. At the same time, it is also advisable to continue traditional treatment: surgical, etiotropic (antibacterial) and symptomatic. Besides, the infusion of exogenous albumin can properly provide pathogenetic therapy while maintaining the amount of complete albumin capable of performing its basic functions. At present, it seems that this is too simple and clear solution. Attention should be paid to the importance of using physical research methods in medical practice, in particular MFS. Within the framework of MFS the fundamental changes in the spectral-fluorescent characteristics of the patient with sepsis were detected for the first time in 2001-2002. It was connected with the changes in the structure of albumin molecules in patients with this disease [2] [6] [7] [8] [9]. Two aspects of the problem of sepsis are very important: the possibility of its early diagnosis and adequate assessment of the risk of disease progression.

The above studies did not pay enough attention to in-depth pathogenetic understanding of the processes that occur in the human body in patients with purulent-septic complications at the molecular level and which were first registered within the MFS. In further research by us, taking into account the above results, the **pathogenetic concept of diagnostic and treatment model of purulent-inflammatory diseases** and sepsis was proposed. It is based on the fact that albumin molecules have the ability to complex. In the diseases which are accompanied by endogenous intoxication, part of the albumin molecules in the blood of patients are blocked by toxins. As a result, there are two types of albumin molecules in their blood: normal (concentration: X) and blocked by toxins/

pathological (concentration: $1 - X$). So, pathological albumin molecules lose the ability to perform their basic functions, namely transport and detoxification. Our proposed pathogenetic concept enabled us to understand better the processes of origin, course and treatment of sepsis.

The new definition of sepsis is to define X^* , i.e. the maximum minimum value of the concentration of albumin in patients with sepsis. If X is more than X^* , this ensures the viability of the organism to some extent. Then at X less X^* , exitus letalis develops. With increasing the severity of the condition of patients the possibility of synthesis of endogenous albumin in their bodies significantly reduces. In order to prevent a decrease of X , it is necessary for patients in severe condition to carry out an infusion of exogenous albumin solution to support properly the body's vital functions. During treatment, the amount of toxins in the blood of patients gradually decreases. This allows us to cancel the infusion of the donor albumin solution at a certain time. At the same time, the process of endogenous albumin synthesis is gradually normalized [15] [16] [19].

It is proposed to use MFS for diagnosis, monitoring and correction of the treatment process. The main characteristics which we study with this method are the fluorescence intensity (I_f) and the position of the maximum fluorescence band (λ_{\max}) of the BS. The main characteristics for the patients with purulent-septic complications are $I_f(X)$ and $(\lambda_{\max})(X)$. They depend on X and are determined by the following interpolation ratios for a mixture of normal and pathological proteins in the BS:

$$\begin{aligned} I(X) &= I_F^a * X + I_F^t * (1 - X) \\ \lambda_{\max}(X) &= \lambda_{\max}^a * X + \lambda_{\max}^t * (1 - X) \end{aligned} \quad (1)$$

They describe the corresponding characteristics for normal (I_F^a , λ_{\max}^a) and pathological (I_F^t , λ_{\max}^t) albumin molecules. We also present the ratio between the lowest excited and main states and the corresponding positions of the maxima of the fluorescence bands of the BS (λ_{\max}) of normal and pathological albumin molecules. We also present the relationship between the energy differences ΔE_a and ΔE_t between the lowest excited and main states and the corresponding positions of the maxima of the fluorescence bands of the BS (λ_{\max}^a , λ_{\max}^t) of normal and pathological albumin molecules.

$$\Delta E_a = hc / \lambda_{\max}^a ; \quad \Delta E_t = hc / \lambda_{\max}^t . \quad (2)$$

where h , c , accordingly, the Planck constant and the speed of light.

Now let us focus on the most interesting of our results obtained within the MFS for patients with sepsis. The introduction of new methods of diagnosis and treatment has always been the driving force of progress in medicine. For such a search to be successful, a scientific approach, a clear statement of the task and hard work were required. To assess the possibilities of using MFS in medical practice, a series of experiments "models of the disease in vitro" was performed [2] [7] [18] [22]. As the result of a thorough analysis of the obtained results, clear trends in the spectral-fluorescent characteristics of the BS were observed.

They were likely to be present in patients with various pathological conditions and could describe changes under the influence of therapeutic measures. Understanding of these patterns and capabilities of MFS made it possible to select patients with such pathologies, in which the changes in the FS of the BS were noticeable and at the same time specific for each of them.

MFS is extremely sensitive method, so its use is promising in the practice of health care facilities. For the successful implementation of this method, it is advisable to create portable devices for measurement of FS of BS of patients and ensure their availability in the health care facilities of research institutions. In order to implement successfully the use of this method in practice, it is necessary to create a database of spectral-fluorescent characteristics of the BS and urine of healthy people; study of the dependence of the spectral-fluorescent characteristics of their BS and urine depending on age, sex, the history of diseases; study of the correlation of the results obtained within the study of MFS, with the data of other laboratory and instrumental methods of diagnosis; conducting a series of new experimental studies to assess the suitability of MFS for diagnosis in surgical and obstetric practice. It is also necessary to create a database of the behaviour of the spectral-fluorescent characteristics of the BS of patients with different diseases of varying severity, including the dynamics on the background of treatment.

3.2.2. Study of Serum Fluorescence Spectra of Donors

The control group in this study was 40 healthy person without chronic diseases, donors aged from 21 to 55 years, whose average age was 36 ± 1.24 years. All of them did not have complaints about their health and did not have any chronic diseases. Among the members of this group were students of high educational institutions, interns, as well as persons who underwent periodic medical examinations (physicians, teachers, workers of the food industry). When people were included in the control group, screening was performed by laboratory examination (general blood test, blood sugar test, general urine test and some biochemical parameters of blood, total protein, bilirubin, urea). Persons who were found to have abnormalities, respectively, were referred to specialists for further examination, and were not involved in the control group.

FS and fluorescence excitation spectra (FES) of BS of donors and 20% donor albumin were studied. Fluorescence intensity was maximal when BS was excited by light with $\lambda_{ex} = 280$ nm, which corresponds to the natural glow of the tryptophan amino acid residue of albumin, and much lower at $\lambda > 300$ nm. Upon excitation of BS and 20% donor albumin in the region of $250 \text{ nm} < \lambda < 280 \text{ nm}$ FS of BS look like a λ -type curves in the region of $300 \text{ nm} < \lambda < 450 \text{ nm}$.

The graphical depiction of the results of the study of the FS of donors and of 20% donor albumin is depicted in **Figure 1**. FS for these objects were found to be quite similar, although the fluorescence band of the donor is slightly wider than the fluorescence band of 20% donor albumin. The position (λ_{max}) of the fluorescence band of the donor depends on his age.

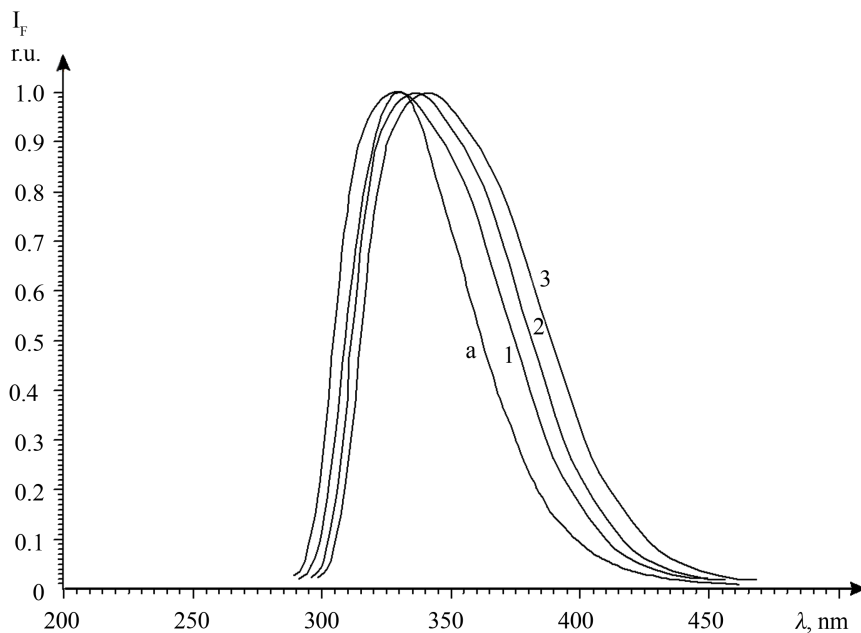


Figure 1. Fluorescence spectra of donor serum (1 - 3) and 20% donor albumin (a) ($\lambda_{ex} = 280$ nm).

In particular, $\lambda_{max} = 328$ nm corresponds to the FS of BS of young donors (1), depicted in **Figure 1**, 342.57 nm—for seniors (3), 337 nm—for the reference donor (2) and $\lambda_{max} = 330$ nm—for 20% donor albumin. It is established, that with age there is a slight shift of λ_{max} of FS BS to the long-wavelength region. The long-wavelength shift of the fluorescence maximum is probably connected with the influence of other components of the BS. The obtained results, as well as the results of the study of “*in vitro* disease models” proved the possibility of using 20% donor albumin as a standard in the study of FS of BS of patients with various diseases.

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

The main task of this section is to study the feasibility and effectiveness of using MFS as an express highly sensitive method of diagnosis, especially early, of sepsis and purulent-inflammatory diseases. For this purpose, FS and FES of BS of donors and patients with sepsis were studied. Very important for us are the results of the study of the spectral-fluorescence characteristics of 20% donor albumin, as well as dilutions of BS with distilled water and 20% donor albumin.

The task of our research is qualitatively different from the approach used in [23]. The authors of the research, presented and discussed in [23], in their study focused on the search of specific spectral-fluorescent quantitative changes in the presence of various pathologies of physiological parameters of the organism, while we focused on the detection of spectral-fluorescent signs of pathognomonic for sepsis and purulent-inflammatory diseases constellation “serum of bacteria”, *i.e.* the phenomenon of bacteremia [6].

FS were studied after exciting the BS with the light $250 \leq \lambda_{\text{ex}} \leq 280$ nm. Such studies were based on our hypothesis [6] about the appearance of special “bacterial proteins” in patients with purulent-septic complications, which occur during the interaction of bacteria and products of their life cycle with albumin [24].

In the study of the spectral-fluorescence characteristics of BS in patients with purulent-septic complications, two probable qualitatively significant tendencies were recorded, namely: the shift of fluorescence band maxima for patients with pre-septic pathology and sepsis in long-wave region and a significant reduction in their intensities (maximum up to 70% - 80%) of the donor unit. Both vectors of change had no correlation with the standard laboratory-biochemical parameters of conventional control of these patients, but correlated properly with the integrated clinical criteria for the severity of the patient's condition and the phenomenon of verified bacteraemia.

The revealed changes in the spectral-fluorescence characteristics of BS in patients with sepsis in most cases were preclinical in nature: they were usually recorded 24 - 48 hours before the appearance of obvious clinical and laboratory signs of a significant change in the general somatic status of patients [25]. At the same time, the structure of the FES of donors and patients with sepsis is generally similar, but the patient's intensity of the excitation spectra is much lower than that of the donor.

In vivo studies include the study of the spectral-fluorescent characteristics of BS of patients with purulent-inflammatory diseases and sepsis. Three main scenarios for the development of sepsis have been identified and described [2] [9]. We will dwell on two of them in more detail (Figure 2 and Figure 3). The results of study of the BS of donor and a patient with severe sepsis caused by purulent epiduritis of the lumbosacral spine and massive retroperitoneal pelvic phlegmon, which was treated in Emergency Hospital from 28.12.2001 to 15.04.2002 are depicted in Figure 1 and Table 1.

At the time of hospitalization, a critically difficult condition of the patient and verified bacteremia (blood seeding at the time of hospitalization: *Staphylococcus aureus*). In the BS of this patient, a long-wave peak ($\lambda_{\text{max}} = 380$ nm, $I_F = 0.3$) (curve 1) was detected, which was associated mainly with the glow of “pathological” albumin molecules [2] [7] [15] [22]. This curve also has a small peak in the region 335 nm. It is associated with the glow of full-fledged albumin molecules and indicates a certain resource for the survival of the patient in such a serious

Table 1. Changes in the spectral-fluorescent characteristics of the serum of a patient with sepsis.

N	<i>d</i>	1	1'	1'	2	3	4	5
Date	28.12.	28.12.	02.01.	02.01.	04.01.	12.02.	19.03.	04.06.
λ_{max} nm	340	380	380	345	345	337	349	340
I_F r.u.	1.0	0.3	0.09	0.15	1.07	0.46	0.39	0.79

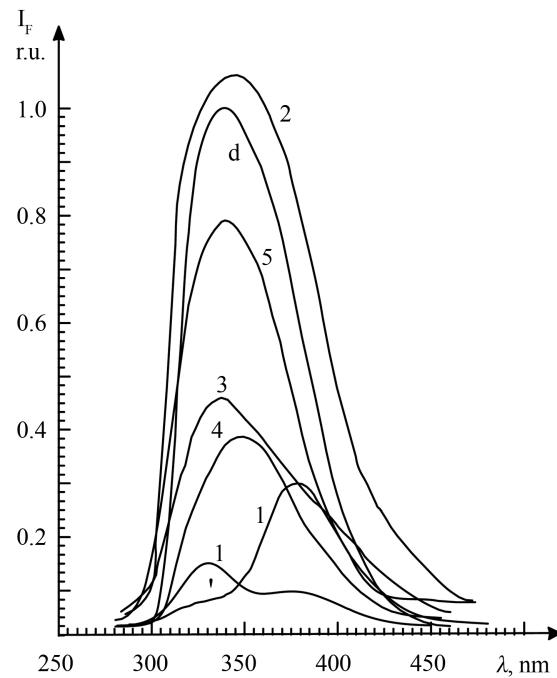


Figure 2. Fluorescence spectra of serum of the person with sepsis who was treated in Emergency Hospital in 2001-2002: 1—28.12.2001; 1'—02.01.2002; 2—04.01.2002; 3—12.02.2002; 4—19.03.2002; 5—04.06.2002 and donor blood serum (d). $\lambda_{ex} = 250$ nm (340 nm—“normal peak”, 380 nm—“septic peak”).

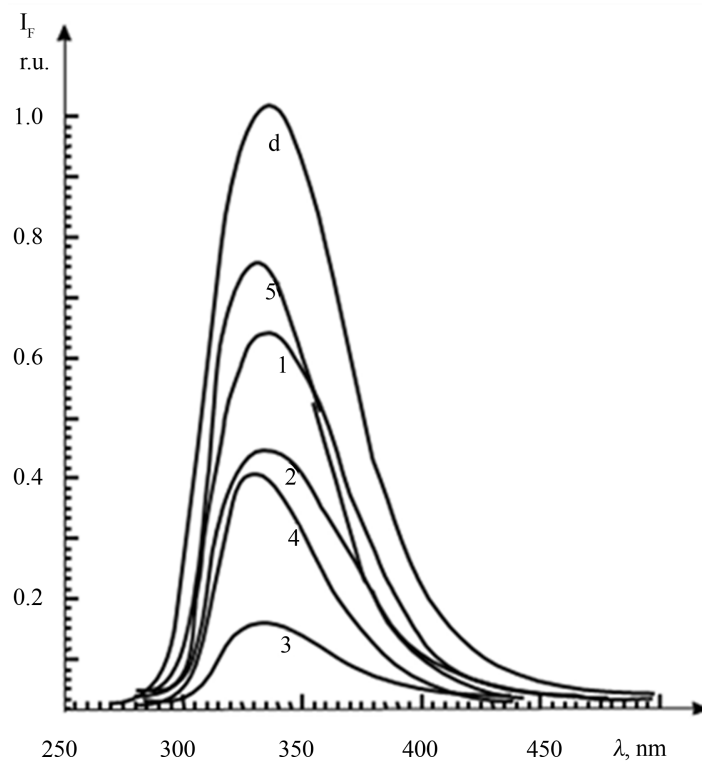


Figure 3. FS of BS of the patient with sepsis-epiduritis, was treated in Emergency Hospital in 2001-2002: 1—03.06; 2—05.06; 3—06.06; 4—07.06; 5—10.06 and donor of BS. $\lambda_{ex} = 280$ nm.

condition. As the result of the in-depth analysis of the situation described above, we modelled the behaviour scenario of FS of BS (growth of X) at 02.01 (curve 1'). The right maximum of this curve indicates a decrease in the concentration of pathological albumin, and the left shows an increase in the concentration of complete albumin in the blood of this patient.

FS of BS of patients in septic condition has a complex nature of behaviour. In particular, in the severe state, it has a two-peak structure (curves 1, 1', which reflects the presence of two varieties of albumin molecules in the BS). **Figure 2** made us possible to illustrate the successful outcome of treating, *i.e.* the patient with sepsis who was admitted to the hospital in a very serious condition. She underwent a complete clinical and laboratory examination, she was prescribed antibiotic therapy and infusion therapy in a volume of 8 - 10 litres daily. At the same time, the results of standard clinical and laboratory data were not informative enough. The patient underwent a thorough examination and surgery to remove the source of infection in the body (massive retroperitoneal pelvic phlegmon, which caused sepsis-epiduritis). Complex infusion, antibacterial, anti-inflammatory therapy was also prescribed, which contributed to the progression of this patient. Undoubtedly, this was facilitated also by her young age (33 years) and the absence of comorbidities. It is also important to note that the survival of this patient in such a serious condition was possible due to $X > X^*$. In this case, although the patient was admitted to the hospital not at the stage of formation of the septic condition, but against the background of its manifestation, MFS helped us to detect septic peak in the long-wave region (**Figure 2**, curve 1) and choose rational treatment tactics.

The suppression of bacteremia helped to reduce the number of pathological albumin molecules in the patient's blood. This in turn contributed to the process of restoring the synthesis of endogenous albumin by the liver. In the next measurement of FS of BS 4.01., (**Figure 2**, curve 2) significantly and at first glance unexpectedly increased the intensity of this band ($1.07 \cdot I_p$). In fact, this process was expected.

At $X \rightarrow X^*$ the peak in the region of 380nm will increase and shift to the long-wavelength region until exitus letalis occurs. In the process of recovery, the "right" peak will decrease and gradually disappear, and the "left" curves 1, 1' gradually increases and slightly shifts to the shortwave region. The above-mentioned possible reorganization of the patient's BS in a severe condition (curve 1, and in the process of recovery curve 1', respectively) may be associated with increased bacteremia, as well as, accordingly, with a positive effect on the patient's health of treatment. Due to the subcompensated changes in the absolute quantitative and qualitative content of BS proteins at the time of the examination (biochemical studies showed total protein and protein fractions at the lower limit of normal), the rapid increase in the fluorescence band of the patient's BS cannot be interpreted by absolute hypoproteinemia, which is inherent in the fluorescence of proteins. The only possible explanation for the above phenomenon of increase in the fluorescence band of the patient's BS fluorescence may be the presence of

daily pre-infusion 8 - 10 liters during this treatment period [6] [7] [26]. Under these circumstances, a regular increase in the fluid component of the BS leads to pseudogipoproteinemia, *i.e.* a laboratory phenomenon that does not manifest with standart biuret reaction and can only be differentiated from true hypoproteinemia by a special Phillips and van Slyke technique (see [6] [7]). In our opinion, the forced excess therapeutic dilution of blood during this period caused the quenching of the fluorescence of the BS of the patient and led to the increase of the intensity of the fluorescence bands of her BS. Undoubtedly, the decrease of septic symptoms had a significant impact on the increase of the fluorescence band intensity of the BS (curve 2). Our in vitro studies of the spectral-fluorescence characteristics of standard dilutions of the donor BS with distilled water (DW) confirmed the correctness of the explanation of the reported phenomenon of the increase in the fluorescence band intensity of the BS of this patient (Figure 2, curve 2) [22]. Besides, the decrease in the content of BS in the samples after the addition of distilled water also led to a significant increase in the intensity of fluorescence bands. Subsequent studies of the fluorescence spectra of this patient showed, that, *i.e.* bacteremia was not completely overcome (Figure 2, curves 3, 4), although the long-wave septic peak disappeared, because the number of pathological albumin molecules has significantly decreased. At that time, the patient's body continued to compete between bacteremia and the compensatory capabilities of her body in combination with comprehensive treatment measures. Only the further long process of treatment under the influence of complex therapy led to the significant suppression of bacteremia and the significant improvement in the patient's condition (Figure 2, curve 5). At the time of the treatment of this patient the pathogenetic model had not been developed yet. Therefore, unfortunately, she was not prescribed infusion therapy with donor albumin solution. We are convinced that this procedure could significantly accelerate the process of recovery of this patient. During the treatment of patients with severe sepsis, it is necessary to examine more often samples of BS of patients in order to prevent their transition to the state $X < X^*$. In this case, it would be possible to reproduce in detail the change in the FS of patients in the state $X \rightarrow X^*$, but only at $X > X^*$. Such studies without the use of donor albumin infusions in the treatment process and with its use would help to improve our knowledge about the possibilities of optimizing the treatment process for patients with sepsis. After leaving the septic state (Figure 2, curves 3 - 5) during recovery, the I_F gradually increases, slightly shifting to the short-wave region. Rather interesting is the study of the behaviour of spectral-fluorescent characteristics of patients with sepsis in the case of using donor albumin infusions in the process of treatment.

Taking into consideration that $h = 6.62 \times 10^{-34}$ Joule-second, $c = 2.99 \times 10^8$ m/second, $\lambda_{\max}^i = 380$ nm and $\lambda_{\max}^a \approx 330$ nm (small peak of curve 1, Table 1), $1 \text{ eV} = 1.6 \times 10^{-19}$ Joule, $1 \text{ nm} = 1 \times 10^{-9}$ m, on the basis of (2) we obtain

$$\Delta E_i = 3.25 \text{ eV}, \quad \Delta E_a \approx 3.75 \text{ eV} \quad (3)$$

So, $\Delta E_a \geq \Delta E_i$.

Very interesting were the results of the study of FS of BS of another patient with purulent epidural lumbar spine, complicated by sepsis, who was treated in Emergency Hospital in June 2002. A significant difference between the two cases is following. For this patient, because of the timely hospitalization and early surgical elimination of the source of infection, the progress of the septic process was much easier, which was significantly reflected in the dynamics by the changes of spectral-fluorescence characteristics (**Figure 3, Table 2**).

Analyzing the results, depicted in this figure, we can observe, that after the elimination of the source of infection on the background of intensive antibiotic therapy in patient with clinically mild sepsis for a certain period there was bacteremia (blood seeding 3-6.06.2002, *Kl. pneumoniae*). Five blood samples were taken for FS testing. The dynamics of FS of BS for this patient were slightly different than for the first patient: the decrease of the intensity of fluorescence bands reached maximum ($0.15 I_F$) only at the end of the bacteremic period (**Figure 3**, curves 1 - 3). At the same time, in this case, there was no significant shift of the fluorescence bands of the BS. It is possible, that in this case, the easier course of the septic process is connected with timely elimination of purulent-septic focus of infection. Subsequently, with the gradual recovery of the patient there was a significant increase in the fluorescence intensity of the BS up to $0.75 I_F$ (**Figure 3**, curve 5).

The comparison of the results of the study of FS of BS and the clinical features of sepsis in the first and second discussed above cases gives background to conclude about the similar nature of the dynamics of recovery in the “postbacterial” period. At the same time, the study of the spectral-fluorescent characteristics of the BS of these patients, in contrast to conventional methods of clinical and laboratory assessment of patients, allowed us to trace clearly the nature of the disease to recovery.

The above results indicate the main most likely scenarios of sepsis. The dynamics of changes of the spectral-fluorescent characteristics of the BS of patients with sepsis objectively reflects the clinical features of the disease, which significantly depends on the quality of diagnosis and correlates with the effectiveness of treatment tactics.

Thus, according to our studies of the BS of patients with sepsis, the decrease of intensity and shift of the fluorescence band are connected with the presence of advanced septic process and correlate with integrated indicators of clinical severity and bacteremia. The dynamics of changes of the spectral-fluorescent

Table 2. Changes in the spectral-fluorescent characteristics of the serum of a person 2 with sepsis.

N	d	1	2	3	4	5
Date	03.06	03.06	05.06	06.06	07.06	10.06
λ_{\max} nm	336	336	334	333	330	331
I_f r.u.	1.0	0.64	0.44	0.16	0.41	0.76

characteristics of BS of these patients quite objectively reflect the course of sepsis and correlate with the effectiveness of treatment tactics.

The results of the study of FS of BS of patients with inflammatory abdominal pathology are depicted in **Figure 4** and **Figure 5**. Some of the curves in these figures for patients in severe condition (in particular, for patients with acute pancreatitis and cirrhosis) have the two-peak structure, which is connected with the presence in their BS of two types of albumin molecules, normal and pathological in significant quantity.

One of the fundamental problems of modern medicine is the significant improvement of the immediate and long-term functional and cosmetic results of surgical treatment of patients with burns. Fundamentally important at the initial stage of the treatment process is the timely restoration of the skin after injury, when patients are not yet exhausted by the long treatment process, and the regenerative properties of the body are still preserved. It is advisable to use lyophilized xeno-implants saturated with silver nanocrystals in order to close burn wounds after their thorough cleaning under general anesthesia [27] [28]. In this case, it is also recommended to activate them with bio-galvanic current, when using auto-, xeno- and dermo-implants [29].

On the background of EI, which occurs in patients with burn injury, tissue repair in the area of inflammation and restoration of homeostasis is sharply complicated. Thus, special attention should be also paid to the problem of complications of burns: sepsis. Taking into account the above results of the study of septic complications in surgical practice, we consider it appropriate to take into

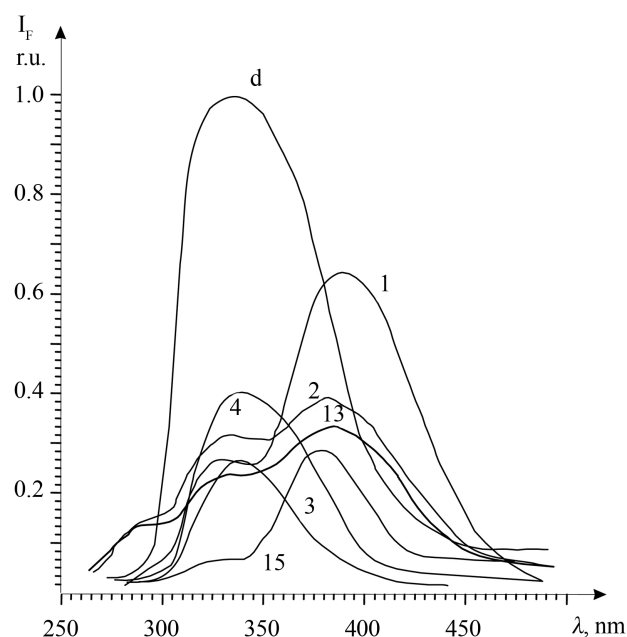


Figure 4. Fluorescence spectra of blood serum of patients with: (a) Acute pancreatitis: 1—12.02.2002; 2—12.02.2002; 3—7.06.2002; 4—19.03.2002; (b) Cirrhosis: 13—12.02.2002; 4—19.03.2002; (c) Sepsis: 15—28.12.2001, who were treated in Emergency Hospital in 2001-2002, and donor blood serum (d); $\lambda_{ex} = 280$ nm.

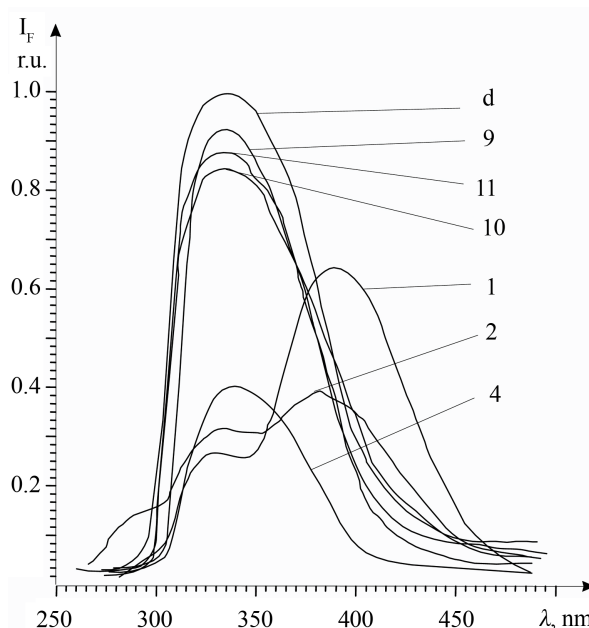


Figure 5. Fluorescence spectra of blood serum of patients with pancreatitis: 9—7.06.2002; 10—4.01.2002; 11—4.01.2002; 1—12.02.2002; 2—12.02.2002; 4—19.03.2002 and donor blood serum (d); $\lambda_{ex} = 280$ nm.

account changes at the molecular level that occur in patients with burn injuries in the case of occurrence of purulent-septic complications. In fact, severe patients with burn injuries can be the model objects during the study of septic conditions in medical practice. The timely verification of sources of infection, reliable diagnosis within the MFS and adequate treatment of patients with burn injuries can prevent their transition to the septic condition [19].

Now we shall illustrate the results of the treatment of one of the patients with the severe burn injury using the approach, proposed by us in this manuscript within the MFS. The results of studies in the dynamics of FS of BS and data for the spectral-fluorescence characteristics of the BS of patient with burn injury, who was admitted to the hospital on the 27th of June, 2015 with the area of the burn surface 38%, are depicted on **Figure 6(a)** and **Table 3(a)**.

In order to compare the spectral-fluorescent characteristics of the BS of patients with burn injury, we shall also present in the relevant figures the results of the spectral-fluorescent characteristics of the patient with sepsis, who recovered after successful treatment (**Figure 3**). *Staphylococcus aureus* 10^5 and *Pseudomonas aeruginosa* 10^6 were verified in this patient on the basis of the microbiological study. He was immediately prescribed appropriate treatment, including antibiotic therapy and infusion therapy with a volume of 2 - 3 liters daily. Due to the infusion therapy, the intensity of FS of BS compared with the fluorescence intensity of albumin ($I_F = 1.00$) did not decrease significantly for several days ($I_F = 0.88$), which correlates with the results of in vitro studies [2] [22]. At the same time, no significant shift of the FS of BS into the longwave region was recorded, despite the verification of several pathogens. At the same time, no significant

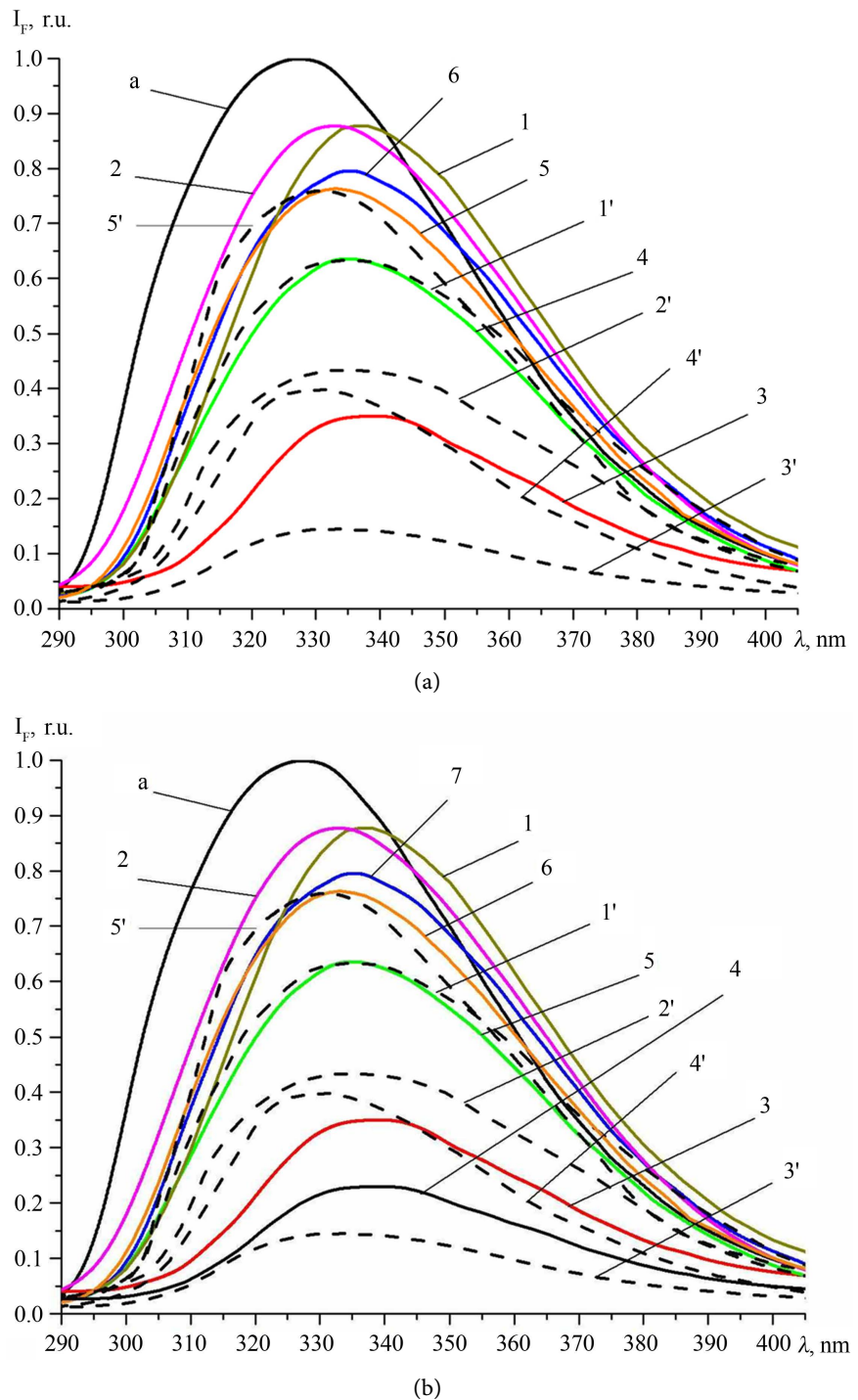


Figure 6. (a) FS of BS of the patient with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2015 in dynamics during the treatment (1—3.07, 2—8.07, 3—13.07, 4—17.07, 5—20.07, 6—24.07) and a patient with sepsis (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06, 5'—10.06), who was treated in 2002 in Ambulance hospital and 20% albumin solution (b), $\lambda_{ex} = 280$ nm. (b) FS of BS of the patient with burn injury, who was hospitalized at Lviv's Communal Clinical Hospital No. 8 in 2015 in dynamics during the treatment (1—3.07, 2—8.07, 3—13.07, 4—17.07, 5—20.07, 6—22.07, 7—24.07) and a patient with sepsis (1'—03.06, 2'—05.06, 3'—06.06, 4'—07.06, 5'—10.06), who was treated in 2002 in Ambulance hospital and 20% albumin solution (b), $\lambda_{ex} = 280$ nm.

Table 3. (a) Spectral-fluorescence parameters fluorescence intensity (I_F) and the position of the maximum (λ_{\max}) of the fluorescence band of the patient. (b) Spectral-fluorescence parameters fluorescence intensity (I_F) and the position of the maximum (λ_{\max}) of the fluorescence band of the patient.

(a)											
N	<i>a</i>	1	2	3	4	5	6	1'	2'	3'	4'
Date	3.07	3.07	8.07	13.07	17.07	20.07	24.07	03.06	05.06	06.06	07.06
λ_{\max} nm	327	336.1	332.2	341.1	335.1	333.1	335.1	335.2	335.2	334.1	331.6
<i>I</i> , r.u.	1	0.88	0.88	0.35	0.64	0.76	0.80	0.63	0.43	0.14	0.40

(b)													
N°	<i>a</i>	1	2	3	4	5	6	7	1'	2'	3'	4'	5'
Date	3.07	3.07	8.07	13.07	17.07	20.07	22.07	24.07	3.06	5.06	6.06	7.06	10.06
λ_{\max} nm	327	336.1	332.2	341.1	341.1	335.1	333.1	335.1	335.2	335.2	334.1	331.6	331
<i>I</i> , r.u.	1	0.88	0.88	0.35	0.27	0.64	0.76	0.80	0.63	0.43	0.14	0.4	0.76

shift of the FS of BS into the longwave region was recorded, despite the verification of several pathogens. Obviously, the intake of sufficient albumin allowed to improve significantly the work of detoxification systems of the body, which had a positive effect on the spectral-fluorescence parameters. Measurements of FS of BS after 10 days after admission to the hospital on the 13th of July, 2015 (**Figure 6(a)**, curve 3), testified to the critical moment, when there was a significant decrease in I_F to 0.35 r.u. and the shift of the FS into the longwave region by 9 nm. This condition of this patient was close to septic (**Figure 6(a)**, curves 3', 4'). This is due to the increased bacteremia in this patient. MFS revealed the deterioration of this patient's condition.

The appointment of the infusion of albumin solution with subsequent complex therapy led to the gradual improvement of the spectral-fluorescent characteristics of the BS (closer to the fluorescence parameters of albumin) in subsequent blood sampling 17.07.-24.07.2015. They correlated well with clinical indicators and the results of laboratory examinations of the patient. Therefore, he was discharged from the hospital in satisfactory condition on the 24th of July 2015.

By controlling the treatment process with the use of infusions of donor albumin solution in the case of deterioration of patient's condition, we can essentially achieve positive completion of the treatment process. The development of septic complications can be very dangerous, especially in patients with concomitant extragenital pathology. The proper organization of the treatment process using infusions of albumin solution, even for patients in serious condition is quite likely to prevent the development of septic complications.

Now we shall illustrate the possibilities of developing the septic condition for the patient, whose FS is presented in **Figure 6(a)**, which may occur with impro-

per organization of the treatment process. The scenario of a possible complicated course of the treatment process for this patient is presented in **Figure 6(b)** and in **Table 3(b)**. **Figure 6(a)** (curve 3) and **Table 3(a)** show that on the 13th of July within the MFS the decrease of the fluorescence intensity and the long-wavelength shift of the FS were recorded. If we do not take into account the data of the MFS on the 13th of July and do not prescribe the infusion of donor albumin, there will be an increase of bacteremia and within the MFS we will get a curve 4 (**Figure 6(b)**). This figure shows that the patient's condition becomes close to septic (curves 4 and 3' are quite close to each other). Therefore, he was prescribed infusion of donor albumin solution several times until his recovery. The scenario of his treatment at the final stage was under the control of the MFS. If donor albumin infusion had not been prescribed on the 17th of July, his health could significantly deteriorate. In this case, infusion therapy with the solution of donor albumin should be continued, although there was no guarantee of successful completion of the treatment process. If there is no ability to monitor the treatment process within the MFS it is necessary to monitor closely the condition of patients and timely adjust the treatment process, timely prescribing infusion therapy with the solution of donor albumin.

4. Conclusions

The deep understanding of the pathogenesis is the key point in the formation of treatment tactics for patients with various diseases. Obtaining information about the mechanisms of origin and evolution of purulent-inflammatory diseases and sepsis is extremely important for the rapid search for effective ways of their prevention and successful treatment. For this purpose, the pathogenetic concept of diagnostic and treatment model of purulent-inflammatory diseases and sepsis was proposed. It is based on the fact, that in patients with these diseases part of the albumin molecules in the blood of patients are blocked by toxins. As a result, there are two types of albumin molecules in their blood: normal (concentration: X) and blocked by toxins /pathological (concentration: $1 - X$). So, pathological albumin molecules lose the ability to perform their basic functions, namely transport and detoxification. Besides, about 6% of albumin molecules in the blood, even in healthy people, are glycosylated. At the same time, in patients with diabetes mellitus with hyperglycemia 9% - 12% of albumin molecules are in the glycosylated state. As a result, the sum of concentrations of pathological and glycosylated albumin molecules is considered pathological.

The new definition of sepsis is to define X^* , i.e. the maximum minimum value of the concentration of albumin in patients with sepsis. If X is more than X^* , this ensures the viability of the organism to some extent. Then at X less X^* , exitus letalis develops.

The main characteristics that we study with this method are the fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{\max}) of the BS. I_F, λ_{\max} are universal markers of the severity of the condition of patients with purulent-inflammatory diseases and sepsis. They are functions of the concentra-

tions of normal (I_F^a , λ_{\max}^a) and pathological albumin molecules (I_F^t , λ_{\max}^t) (1). The peculiarities of the behaviour of these markers for purulent-inflammatory diseases, sepsis and burn injuries have been studied and illustrated. Regardless of the etiological factors of the septic condition in the patient's body, the processes that take place in it, occur in the similar scenario. The study of the biological objects within the MFS is allowed to detect pathological processes in living organisms at an early stage of their development. To overcome EI, it was proposed to use infusions of 20% solution of donor albumin. In particular, in Lviv's Communal Clinical Hospital No. 8 using treatment tactics, developed within the MFS (Ph.D. V. Savchyn, N. Tuzyuk) during the pandemic of COVID-19 in 2020-2021 more than 35 patients with burn injuries, including those in serious condition, were successfully cured even without the use of MFS.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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