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MICROSCOPIC ASPECTS OF THE DIAGNOSTICS OF PURULENT-SEPTIC COMPLICATIONS IN MEDICAL PRACTICE

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INTRODUCTION

Over the last thirty years, much attention has been paid to the problem of the diagnostics and treatment of sepsis. According to the definition of the Third International Consensus on the Definition of Sepsis and Septic Shock (sepsis-3, 2016), sepsis is a dangerous dysfunction of internal organs caused by the dysregulation of the body's response to infection[1]. Sepsis, initiated by a pathogen, most often bacteria, leads to an inflammatory process that has a harmful effect on the entire human body. This pathophysiological response can culminate in multiple organ failure, usually due to the combination of cardiovascular, cellular, coagulation and endothelial dysfunction[2].

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 was changed three times. The international protocol of their intensive therapy is periodically updated with the participation of dozens of leading organizations and experts[3]. Unsatisfactory results of treating sepsis were directly related to the lack of effective techniques for its express diagnosis, especially the early one. At the same time, insufficient attention was paid also to the pathogenetic assessment of the development of purulent-septic complications. The systemic response will progress and lead to the organ dysfunction, septic shock and eventually to the irreversible condition without effective treatment. Sepsis is a leading cause of death worldwide: 48.9 million cases of sepsis were registered in 2017, in particular, accounting for 20 % of all deaths

[1] Singer M., Deutschman C. S., Seymour C. W., et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8): 801–810.

[2] Seymour C. W., Liu V. X., Iwashyna T. J., Brunkhorst F. M., Rea T. D., Scherag A., et al. Assessment of clinical criteria for sepsis for The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315:762–74.

[3] Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021 Critical Care Medicine: November 2021. – Volume 49 – Issue 11. – P. e1063-e1143. doi: 10.1097/CCM.0000000000005337

worldwide[4]. The tactics of previous studies about sepsis were mainly aimed at evaluating the clinical state of the organism and some laboratory indicators.

The molecular basis of organ failure remains unclear, sepsis is characterized mainly by six types of organ dysfunction: neurological (changes in mental status), pulmonary (hypoxemia), cardiovascular (shock), renal (oliguria and/or increased creatinine concentration), coagulation disorders (decreased platelet count) and liver (hyperbilirubinemia). The mechanism underlying the dysfunction of tissues and organs in patient with sepsis is apparently the decrease in oxygen delivery to cells and their utilization, with further increase in anaerobic glycolysis and lactic acid production, reduced deformability of erythrocytes, thrombosis of microvessels[5]. All of these mechanisms, combined with systemic hyperinflammation and persistent immunosuppression, generalized increased catabolism, insulin resistance, and hyperglycemia can contribute to damage at the cellular level. A lot of immune and non-immune mediators are involved in pathogenesis. The main problems are endothelial dysfunction, coagulation disorders, changes in cellular function, and dysregulation of the cardiovascular reactions[6].

The peculiarities of the course of this disease were analyzed in detail and it became obvious that without global fundamental research, it is almost impossible to achieve significant progress in this very difficult area of medicine, according to which it was recommended to focus primary attention on improving diagnostics and the search for new markers, as well as improving treatment tactics and monitoring the condition of patients in the course of treatment. These international efforts have led to earlier diagnosis and treatment of sepsis, resulting in improved patient survival.

The treatment of burn diseases and burn sepsis remains one of the tough problems of modern medicine. There are differences between sepsis in

[4] An Improved Mathematical Model of Sepsis: Modeling, Bifurcation Analysis, and Optimal Control Study for Complex Nonlinear Infectious Disease System Yuyang Chen, Kaiming Bi, Chih-Hang J. Wu, David Ben-Arieh, Ashesh SinhaarXiv: 2201.02702 [math.DS(or arXiv:2201.02702v1 [math.DS] forthisversionhttps://doi.org/10.48550/arXiv.2201.02702 7 Jan 2022].

[5] Oxidative stress and mitochondrial dysfunction in sepsis H. F. Galley *BJA: British Journal of Anaesthesia*, Volume 107, Issue 1, July 2011, Pages 57–64, https://doi.org/10.1093/bja/aer093

[6] Drosatos K., Lymperopoulos A., Kennel P. J., Pollak N., Schulze P. C., Goldberg I. J. Pathophysiology of sepsis-related cardiac dysfunction: driven by inflammation, energy mismanagement, or both? *Curr Heart Fail Rep*. 2015; 12 (2): 130–140. doi: 10.1007/s11897-014-0247-z

surgical patients in general and sepsis in burn patients[7]. Burn patients lose their first barrier to infection: their skin. Patients with widespread burns are exposed constantly to inflammatory mediators, while the wound remains uncovered by its own skin. And when the area of the burn lesion is more than 40–50 % of the body surface, the influence of mediators and pathogens lasts for months[8, 9].

The modern medical care for patients with burns is an unprecedented indicator of patient survival compared to previous years. The most common complications of burn disease are septic complications. Although tremendous efforts have been made to improve the early diagnostics and treatment of sepsis in the general population, very little progress has been made in the management of sepsis in burn patients. Burn patients have persistent SIRS. This is why they are always excluded from any sepsis research, including Sepsis-3 and the Surviving Sepsis 2016 campaign[10]. Studies have shown that the earlier symptoms of sepsis are detected and treatment begins, the better is the outcome [11].

Timely restoration of the skin after the injury is important fundamentally for patients with burns, when they are not yet exhausted by the long treatment process, and the regenerative properties of the body are preserved[12]. It is advisable to use lyophilized xenoimplants saturated with silver nanocrystals in order to close burn wounds after excision of necrosis under general anesthesia. At the same time, auto-, xeno- and dermoimplants

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should be also activated by biogalvanic current[13]. Against the background of endogenous intoxication (EI), which occurs during a burn injury, the repair of tissues in the inflammation zone and the restoration of homeostasis are sharply complicated[14]. In recent years, the role of modern methods of the diagnostics of sepsis has grown significantly. The diagnosis of infectious complications is primarily based on the clinical picture and data of diagnostic methods. The general blood test with a leukocyte formula is the most accessible method of diagnosing inflammatory processes. However, there is no sufficiently reliable evidence of the clinical role and diagnostic reliability of leukocytosis in confirming the appearance of the postpartum infection[15]. No reliable correlation has been established between leukocytosis and the bacterial infection.

Rational management of the early postoperative period is very relevant in the clinical practice of surgeons. Prevention of purulent-inflammatory complications and EI syndrome are important. The role of various laboratory methods in the diagnosis of purulent-inflammatory diseases remains important until now. At the same time, clinical and laboratory signs of the systemic inflammatory reaction are not sufficiently reliable criteria, especially for their early diagnosis.

The problem of diagnosis has always been a priority area of medical research. After all, this is the key to timely and effective treatment, recovery and survival of patients. This applies especially to the effective modern early diagnosis of sepsis, which would allow the rapid initiation of successful treatment. The special efforts of doctors were focused on the search for biomarkers that, in their opinion, can most fully take into account the specifics of the course of this serious disease and help in its diagnosis and successful treatment[16].

The development of sepsis was believed previously to be a sequential process of activation of first pro-inflammatory mediators, and then anti-inflammatory ones. Today, it has been proven that both pro- and anti-

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inflammatory cytokines are activated in patients with sepsis simultaneously[17].

The sensitive biomarkers of systemic inflammation are cytokines (interleukins: IL-1, IL-6, IL-8, IL-10, IL-12), tumor necrosis factor (TNF-α), platelet activation factor (PAF), transforming growth factor-β (TGF-β), presepsin (PSP), lactate, as well as C-reactive protein (CRP) and procalcitonin (PCT). TNF-α is the first triggering pro-inflammatory cytokine and IL-10 is an important anti-inflammatory[18]. The results of the search will be considered successful if the identification of biomarkers is available for routine clinical use. A biomarker, which meets all these requirements, has not been identified yet[19].

The "Achilles heel" recognized by the medical society in the diagnosis of sepsis is the sufficiently long period of waiting for clinical and laboratory symptoms and the results of bacteriological studies. This is, in fact, a time of the lost therapeutic opportunities and postponement of the adequate treatment. The diagnosis of sepsis should include the following characteristics: rapid detection, minimal invasiveness, high sensitivity and specificity for the immediate initiation of antibiotics in the case of presence of symptoms of systemic inflammation.

Unfortunately, most of modern research methods are representative against the background of already manifesting manifestations of pathological processes. This indicates that it is necessary to have a method that would offer high sensitivity and the possibility of reliable diagnosis even at the initial stage of the development of diseases and providing a prognostic assessment of their course. The progress of science and technology in the second half of the 20th century led to the widespread use of physical methods for the diagnostics of various diseases. Basic research over the past several decades has shown that spectral fluorescence was the most versatile method in biological spectroscopy[20].The main advantages of this method are high sensitivity, accuracy, expressiveness and simplicity of fluorescent

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characteristics. These signs led to a special interest to fluorescent analysis as an important method of modern, and especially early, diagnosis of purulent-inflammatory diseases and sepsis[21].

Insufficient attention was paid to the microscopic processes occurring in the bodies of patients with this condition for a long time. Thus, traditional schemes were used in the treatment. After all, excessive attachment to the monitoring of the external signs of the clinical picture of the patient with sepsis does not provide the opportunity to analyze the changes in his blood serum (BS) at the molecular level in details. So, it did not lead to the improvement of traditional treatment regimens. For example, a number of papers have shown that the use of albumin potentially leads to a decrease in mortality in patients with severe sepsis[22]. Only volemic? Is there another mechanism? But it was impossible to detect real changes in the structure. The most widely studied biomarkers do not predict sepsis in burn patients effectively. Procalcitonin was moderately sensitive (73 %) and specific (75 %) for sepsis in burn patients. C-reactive protein was highly sensitive (86 %), but not specific (54 %). WBC count had low sensitivity (47 %) and moderate specificity (65 %)[23].

EI significantly deepens in septic patients. At the same time, the albumin molecules in the blood turn into a partially blocked system[24]. Albumin molecules perform transport, detoxification, antioxidant and ligand-binding functions[25].

This is a complex mechanism. It is necessary to find ways to preserve the vital activity of the body with such pathological changes. The pathogenesis

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of the development of this phenomenon has not been analyzed and described. A deep understanding of the above-mentioned processes led to the creation of the pathogenetic concept and a reasonable approach to solve an important problem: if full-fledged albumin in patients with sepsis becomes less and less, then in order to replenish its reserves in human blood, it is advisable to carry out exogenous albumin infusions. At the same time, it is advisable to continue the traditional treatment: operative, etiotropic and symptomatic. Albumin infusion allows us to provide the pathogenetic therapy by replenishing the amount of albumin capable of performing detoxification and transport functions and restoration of the protein supply in the body. At first glance, it seems that this is too simple, but an understandable solution. Attention should be paid to the importance of physical research methods in medical practice, in particular MFS[26].

In 2001, systematic studies of BS of patients with purulent-inflammatory diseases and sepsis within the framework of MFS began in Lviv (Ukraine) on the initiative of Prof. I. Herych[27, 28]. This method is the most versatile method in biological spectroscopy[29]. Further research within the framework of the MFS was devoted to the problems of purulent-inflammatory complications and sepsis, as well as acute abdominal pathology and combustiology[30, 31].

In this paper the main attention is paid to the discussion and analysis of the results of scientific research that we have received, which relate to the development of purulent-septic complications. Problems of tactics and the latest technologies of surgical treatment of patients with burn injuries,

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[27] The New Approach to the Diagnostics and Treatment of Endogenous Intoxication in Patients with Burn Injury / S. Zaporozhan, V. Savchyn, L. Ostapiuk, A. Voloshinovskii, N. Tuziuk, and T. Malyi // International Journal of Clinical Medicine. – 2020. – 11. – P. 375–388. doi: 10.4236/ijcm.2020.116033

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[31] Ostapiuk L. (2022) The Pathogenetic Concept of the Diagnostic-Treatment Approach for Patients with Purulent-Septic Complications. *International Journal of Clinical Medicine*, 13, 1–21. doi: 10.4236/ijcm.2022.131001

a thorough analysis of the current state of early diagnosis of septic diseases, and problems of managing the treatment process using MFS and other biomarkers in order to significantly improve the treatment process to prevent septic complications.

1. Actual problems of modern combustiology

Burns occupy one of the important places in the structure of traumatism. In the late 20th century, they accounted for 6.6 % to 14.0 % of all types of injuries[32] In Ukraine, about 50,000 people suffer from heat damage every year, among which 9,000 are children[33]. Treatment of victims with extensive burns is associated with difficulties, because despite the implementation of the achievements of resuscitation, intensive care, respiratory support, the frequency of development of multiple organ failure (MOF) and septic complications remains quite high. Over the past 30 years, significant advances have been made in the treatment of patients with extensive burns according to improvements in resuscitation and wound care, resulting in an expanded contingent of recovering burn victims[34]. At the same time, severe thermal injury and damage of deep anatomical structures become the causes of partial or complete disability of 21–28 % of victims[35]. The main factors of mortality are the development of the systemic inflammatory process, MOF and infectious complications[36].

The relevance of the problem of treating burn diseases is determined by the severity of the injury, damage to many organs and systems, the inevitable development of MOF, the duration of treatment, economic costs, a sharp deterioration of the quality of life of patients who have suffered long-term burn disease (BD) and the presence of high mortality.

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[34] Rasmussen J., Erdogan M., Loubani O., Green R. S. Successful Use of Extracorporeal Membrane Oxygenation Therapy in Patients With 80 % Full Thickness Burns. J Burn Care Res. 2021 Mar 4; 42 (2):345–347. doi: 10.1093/jbcr/iraa160. PMID: 33057616

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Sepsis and septic shock are the main causes of mortality in patients with severe thermal injury. The overall mortality in patients with burn sepsis does not tend to decrease. The search for markers for early diagnosis of infectious complications in patients with extensive burns continues. The specificity of thermal injury is connected with the triggering effect of a burn lesion on the development of an inflammatory reaction, which is reflected both in the phase course of the wound process and in the staging of the manifestations of the burn disease. Massive endogenous histogenic-resorptive intoxication causes the depletion of natural resistance factors and immunological reactivity[37].

The thermal injury is accompanied with the hyperinduction level of functioning of the cytokine system in the body, accompanied with the release of a large number of various cytokines[38]. The plasma of a burned person becomes toxic and can damage blood cells. Tissues and individual substances in the body of a burned person, circulating immune complexes acquire antigenic properties. Antibodies to one's own cells and blood cells appear.

The main causes of high mortality are purulent-septic complications associated with the conditions of the development of an inflammatory reaction in the burn wound zone, long-term rejection of the necrotic scab, and a decrease of the level of natural resistance and immunological reactivity of the body.

However, in patients with severe burns, the systemic inflammatory process becomes uncontrolled, leading to increased inflammation that does not cause healing, but rather causes a generalized catabolic state and delayed healing. This response is almost unique for burns and is called the hypermetabolic response; it is associated with catabolism, increased rates of organ failure, infections, and even death[39].

The direct cause of the mortality of patients with severe burns is sepsis, which is associated with damage of many organs and systems as a result of the development of a severe burn disease and septicotoxemia, the untimely provision of specialized intensive therapy (IT) in the stage of BS (burn shock), as well as the delay of the use of modern surgical technology for

[37] Kovalenko O. M. The influence of the wound process on the formation of a systemic inflammatory response and early sepsis in patients with burns in the acute period of burn disease Kozynets G. P., Osadcha O. I., Kovalenko O. M., Linnyk O. M. Modern medical technologies. – 2019. – № 2 (41) part 3. – P. 13–21.

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skin restoration cover. In addition, the untimely identification of microbial agents and the use of antimicrobial drugs without local action[40].

Despite the severe course of the burn disease, patients usually survive now. This is partly due to the early excision of non-viable tissues and auto-, allo-, xenoderm transplantation, implementation of the intensive therapy protocols and provision of nutritional and metabolic support[41].

Burn necrotic scab on wounds is a source of infection and intoxication; hence, it should be removed as soon as possible, before the development of severe EI, while the adaptive capabilities of the body are preserved and the patient is not exhausted by a long course of BD[42].

The development and introduction of new methods of wound treatment into clinical practices have contributed to the improvement of treatment, allowing the establishment of standard treatment regimens. These regimens range from early excision of necrotic tissue to the use of a cultured epithelial autodermal graft. However, even excision of necrotic tissues early after the injury does not prevent the development of septic complications in many cases. For this aim, it is necessary to determine the response of the victim's immune system to the injury and other biological markers.

The need to improve patient comfort, infection control and epithelialization rates has led to the development of various alternative treatments for superficial (partial thickness) burn wounds over the past three decades. Semi-occlusive and synthetic membranes are the most important clinically applicable wound dressings. There is no need for frequent dressing changes, because epithelization continues under partially occlusive dressings[43].

The modern surgical approach to the treatment of deep burns involves early excision of the entire thickness of the burn necrotic tissue followed by early closure of the wound, preferably with an autologous skin graft. As

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[43] Marc G. Jeschke, M. D., PhD, Shahriar Shahrokhi, M. D., Celeste C. Finnerty, PhD, Ludwik K. Branski, M. D., Manuel Dibildox, M. D. The ABA Organization & Delivery of Burn Care Committee, Wound Coverage Technologies in Burn Care: Established Techniques, Journal of Burn Care & Research, Volume 39, Issue 3, May/June 2018, Pages 313–318, https://doi.org/10.1097/BCR.0b013e3182920d29

early excision and coverage of the burn wound has become routine now, the risk of serious systemic infection from the burn wound has been reduced[44].

Early excision, performed after resuscitation and stabilization of the patient, usually within 48–72 hours of the burn, reduces blood loss and post-burn morbidity and mortality significantly[45]. The vast majority of specialists believe that the most favorable period for surgical treatment of dermal burns is 2–3 days after the injury.

In the case of widespread superficial and deep burns, early excision is accompanied by temporary closure of the wounds with xenoderm implants or synthetic coatings. The use of lyophilized xenoderm implants activated by biogalvanic current is especially effective. The technique of early necrotomy with xenodermoplasty prevents the progressive intoxication from the affected areas and the development of infection in the wounds, reduces the possibility of further progression of the burn disease and leads to the restoration of the skin in the shortest possible time.

The technique of early necrotomy with xenodermoplasty prevents progressive intoxication from the affected areas and the development of infection in the wounds, reduces the possibility of further progression of the burn disease and leads to the restoration of the skin in the shortest possible time.

The threat of developing of sepsis in burn patients remains until the skin is restored completely. Although the criteria for the development of sepsis correspond to the generally accepted ones, the fact that the development of a systemic inflammatory response begins from the first days of a burn disease should be taken into account. This significantly distinguishes burn sepsis from sepsis in the intensive care population and complicates its diagnosis and treatment[46].

In general, infection prevention strategies such as early excision and transplantation, aggressive antimicrobial therapy, and early enteral nutrition improve survival[47]. But despite advances in antimicrobial therapy, the number of deaths associated with multiple antibiotic-

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resistant microorganisms has increased. Patients with thermal trauma have syndromes of systemic inflammatory response, hypermetabolism-hypercatabolism and possible manifestations of organ failure before wound closure. Early diagnosis of sepsis is very important for the rapid initiation of adequate treatment.

This is why numerous studies are directed at finding and developing an accurate algorithm for the diagnosis of burn sepsis. The doctors' decisions will be more justified if they have the results of accurate biomarkers that reflect the diagnosis or the evolution of inflammatory processes in a severely burned patient.

An ideal biomarker of infection should combine diagnostic, prognostic and subsequent therapeutic characteristics and should be available rapidly and in time for routine clinical use[48]. For residents of low-income countries, it is not possible to provide a full-fledged examination of the immune system with determination of the level of cytokines, which does not allow to predict and diagnose sepsis in time. More than a hundred biomarkers have been studied in the blood serum of patients with sepsis. However, only some of them are useful to participate in clinical practice[49]. Despite modern advances in prevention and treatment, sepsis remains the leading cause of death in patients with severe burn injury[50].

2. Biomarkers of purulent-inflammatory diaseases

In this section, we will dwell on the most important information about biomarkers and discuss the possibilities of their use for the diagnosis of purulent-septic complications. At the same time, we will use the information presented in the papers[51, 52] to a considerable extent.

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[49] Standage S. W., Wong H. R. Biomarkers for pediatric sepsis and septic shock. Expert Rev Anti Infect Ther. 2011 Jan; 9 (1):71–9. doi: 10.1586/eri.10.154. PMID: 21171879; PMCID: PMC3033193.

[50] Comparative assessment of microbiological studies and the terms of infection of burn wounds with conditionally pathogenic microflora. V. I. Nagaychuk. – Surgery of Ukraine, 2015. – irbis-nbuv.gov.ua

[51] Faix J. D. Biomarkers of sepsis Crit Rev Clin Lab Sci. 2013 Jan-Feb; 50 (1):23–26. doi: 10.3109/10408363.2013.764490. PMID: 23480440 Free PMC article. Review

[52] Predicting and managing sepsis in burn patients: Current perspectives. Omar Nunez, Lopez Janos, Cambiaso-Daniel Ludwik K. Branski, William B. Norbury, David N.

C-reactive protein (CRP) is encoded by the CRP gene, located in humans on the short arm of the first chromosome. It was discovered by Taillett and Francis in 1930. The length of the polypeptide chain of this protein is 224 amino acids, and the molecular weight is 25.039 Da. It is a classic acute-phase protein and it has a place for binding metal ions. It got its name due to its ability to bind C-polysaccharide (LPS) of the pneumococcal cell wall, i. e. to enter into an immune reaction with it. CRP is synthesized mainly by liver cells (hepatocytes), activated by IL-6. It consists of five identical polypeptide chains[53]. CRP is the most sensitive of the markers of the acute phase, and its concentration increases rapidly during the progression of the inflammatory process. The appearance of CRP precedes often the appearance of clinical symptoms, including fever. In healthy people. CRP is a trace protein, and after the appearance of an acute-phase response, its concentration in the BS increases rapidly. At the same time, the increase begins within 6–12 hours, and the peak value is reached within 24–48 hours. CRP levels above 100 ng/ml are associated with marked effects, including severe injury and infection (sepsis). The elevation of CRP in patients with infection may be less pronounced in patients with liver disease.

CRP has proven itself as a marker of infection and/or inflammation[54]. This is one of the group of reagents of the acute phase of the proteins mentioned above. Some of these proteins play a supporting role and enhance inflammation (ex, complement), while others protect likely the host from inflammatory tissue damage. CRP levels rise much more significantly during acute inflammation than levels of other acute-phase reactants. This is why this test has been used for many decades to detect serious inflammatory or infectious diseases, especially in pediatrics and more recently as a biomarker of inflammation accompanying atherosclerosis[55] and cardiovascular diseases[56]. It is, of course, used to screen for early sepsis that occurs within

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Herndon ther clin risk manag pubmed 2017 Aug 29; 13: P. 1107–1117. PMCID: PMC5584891PMID: 28894374. DOI: 10.2147/TCRM.S119938. ECOLLECTION 2017.

[53] Effects of simvastatin on C-reactive protein in mixed hyperlipidemic and hypertriglyceridemic patients / H. E. Bays, E. A. Stein, A. K. Shah et al. // Amer. J. Cardiology. – 2002. – V. 90, № 9. – P. 942–946.

[54] Gabay C., Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Eng J Med 1999; 340:448–54 [Crossref], [PubMed], [Web of Science®], [Google Scholar].

[55] Jaye D. L., Waites K. B. Clinical applications of c-reactive protein in pediatrics. Ped Infect Dis 1997; 16:735–8 [Google Scholar].

[56] Benzaquen L. R., Yu H., Rifai N. High-sensitivity C-reactive protein: an emerging role in cardiovascular risk assessment. Crit Rev Clin Lab Sci 2002; 39:459–97 [Taylor & Francis Online], [Google Scholar].

the first 24 hours of life[57], as its sensitivity is generally considered very high in these cases. CRP is also often used to monitor patients after surgery.

The presence of an elevated concentration of CRP in BS is usually an important prognostic indicator indicating the presence of bacterial or viral infection, sepsis, tissue damage and diabetes. It is the most sensitive indicator of tissue damage during inflammation, necrosis and trauma. At the same time, it is produced in response to infectious agents entering the human body, trauma and systemic connective tissue diseases (rheumatic diseases). CRP stimulates immune reactions in the patient's body, activates his defense systems and has a high correlation with the activity of the disease, that is, its concentration becomes higher during the more active stage of the inflammation (infectious or autoimmune) and wider in the area of tissue damage in case of necrosis or trauma. It has been established that CRP in blood is an indicator of the acute phase of pathological and inflammatory conditions. It reacts almost instantly to the corresponding changes in the patient's body. At the same time, its level gradually increases immediately in response to the further progression of the disease, trauma, and also decreases quickly when the patient's condition normalizes. CRP is one of the factors of humoral immunity, which consists of the activation of the body's immune reactions, binding of various microorganisms and decay products of damaged tissues. Determining the level of CRP is important for diagnostic examination in the standard volume of therapy together with delaying the appointment of antibiotics to improve the results of treatment. An immunoturbidimetric method with latex amplification is used in order to detect CRP in the blood. It is a fairly widely used biomarker in clinical practice.

Procalcitonin (PCT). The papers [58, 59, 60] noted the diagnostic value of PCT determination as one of the diagnostic markers of purulent-inflammatory diseases and sepsis. It is currently widely used in clinical practice. This polypeptide of 116 amino acids is a calcitonin prohormone and is encoded by the CALC-1 gene. In normal conditions, PCT is produced by neuroendocrine cells, mainly in the thyroid gland (C cells), where it undergoes changes to form calcitonin, which regulates calcium

[57] Hofer N., Zacharias E., Muller W., Resch B. An update on the use of C-reactive protein in early-onset neonatal sepsis: current insights and new tasks. Neonatology 2012; 102:25–36 [Crossref], [PubMed], [Web of Science®], [Google Scholar].

[58] Bohuon C. A brief history of procalcitonin / C. Bohuon // Intensive Care Med. – 2000. – V. 26, Suppl. 2. – P. 146–147.

[59] Procalcitonin: a new laboratory diagnostic marker of sepsis and purulent-septic complications in surgery / B. R. Gelfand, M. I. Filimonov, T. B. Brazhnyk [and others] // Bulletin of intensive therapy. – 2003, No. 1, 2.

[60] Schlattmann P., Brunkhorst F. M. Procalcitonin as a diagnostic marker for sepsis. Lancet Infect Dis. 2014; 14 (3):189.

metabolism. It is also produced in small amounts in a number of other neuroendocrine cells of the GI tract and lungs, but is, of course, suppressed in neuroendocrine tissues. The bacterial infection stimulates the CALC-1 gene, which leads to an increase in PCT production. The main inducers of PCT synthesis are endotoxins, LPS and pro-inflammatory cytokines IL-6, TNF-α. The level of PCT increases already 3 hours after the appearance of a bacterial infection, reaching a peak after 20 hours. After the suppression of the infectious process, the PCT level decreases by approximately 50 % daily. The noticeable change of PCT in the septic area in comparison with other indicators of bacterial infections allows to use PCT as the biomarker of bacteremia and sepsis since 1990. The widespread availability of PCT testing over the past few years may have somewhat reduced the importance of CRP as a sepsis biomarker. PCT is the precursor of mature procalcitonin, a hormone that has significant physiological effects on humans but is capable of lowering plasma calcium levels. In the early 1990s, researchers found elevated PCT levels in patients with an invasive bacterial infection[61]. Subsequent studies have shown that a number of tissues throughout the body, but not just cells at the local source of infection, produce PCT[62]. Like CRP, PCT can also have a pro-inflammatory effect[63]. An expert recommended PCT as a useful test for critically ill patients who develop a new fever[64]. Most commercially available PCT assays have been approved. Over the past decade, numerous investigators have studied the diagnostic value of PCT in comparison with the corresponding data for CRP. Out of 49 studies, 15 of them evaluated results based on PCT and CRP simultaneously[65]. The conclusion is that both approaches are effective, although the odds ratio for PCT (14.69) was significantly higher than for CRP (5.43). An increase of PCT concentration

[61] Assicot M., Gendrel D. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993; 341:515–8 [Crossref], [PubMed], [Web of Science®], [Google Scholar].

[62] Muller B., White J. C., Nylen E. S., et al. Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. J Clin Endocrinol Metab 2001; 86:396–404 [PubMed], [Web of Science®], [Google Scholar].

[63] Tavares E., Minano F. J. Immunoneutralization of the aminoprocalcitonin peptide of procalcitonin protects rats from lethal endotoxaemias: neuroendocrine and systemic studies. Clin Sci 2010; 119:519–34 [Google Scholar].

[64] O'Grady N. P., Barie P. S., Bartlett J. G., et al. American College of Critical Care Medicine; Infectious Diseases Society of America. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med. 2008; 36: 1330–40. – PubMed.

[65] Uzzan B., Cohen R., Nicolas P., et al. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Crit Care Med. 2006; 34:1996–2003. – PubMed.

is observed in patients with systemic inflammation of bacterial etiology, which occurs in patients with severe bacterial infections and sepsis. At the same time, PCT reaches peak values earlier than CRP. At the same time, it is believed that a change in its level does not necessarily reflect the presence of an infection and the real dynamics of the inflammatory process in patients with hemodynamic instability.

The immunoluminometric method (LUMItest PCT, BRAHMS Diagnostica GmbH, Berlin, Germany) is used to determine the concentration of PCT in blood plasma. This method is based on the reaction of two highly specific monoclonal antibodies with two positions of the PCT molecule (calcitonin and catacalcitonin). At the same time, cross interaction is excluded. As a result, antigen-antibody complexes fixed reliably to the wall of the test tube are formed. The analytical sensitivity of the method is 0.1 ng/ml, and the functional sensitivity is 0.3 ng/ml (internal error of the method). PCT test has an important diagnostic value in determining the prognosis of the disease. It helps to carry out differential diagnosis of sterile and infected forms of pancreatic necrosis, to determine indications for relaparotomy, to differentiate "pseudosepsis" from a fever syndrome of unknown origin, to determine indications for high-cost treatment methods (extracorporeal methods).

Tumor necrosis factor-α (TNF-α) is one of the studied thoroughly pro-inflammatory cytokines. This protein is encoded by the gene of the same name, located in humans on the short arm of the sixth chromosome. The length of the polypeptide chain of this protein is 233 amino acids, and the molecular weight is 25.644 Da. It is produced by several types of cells (mainly activated macrophages, to a lesser extent synthesized by other types of cells (CD4+-lymphocytes, NK-cells, neutrophils, danger cells, eosinophils, neutrophils)) in response to the action of bacterial products of endotoxins and hypoxemia by activating the system of complement. It is localized in the cell membrane. The synthesis of TNF-α in non-activated cells does not occur, i. e. in the body of a healthy person in the blood serum TNF-α is not defined. The protein coded by the gene belongs to the cellular signaling proteins (cytokines, phosphoproteins), participates in the processes of systemic inflammation, and is one of the cytokines that form the acute phase reaction. The activation of mRNA synthesis in macrophages and mononuclear leukocytes occurs under the influence of toxins, bacteria, viruses, and circulating immune complexes. TNF-α belongs to the non-specific pro-inflammatory cytokines of the first phase of inflammation, the level of which begins to rise in the first hours after the onset of systemic inflammation. This biomarker is involved in the induction of apoptosis and cell survival, causes vasodilation, also induces the production of nitric oxide, promotes chemotaxis of neutrophils and activates prothrombic and

fibrinolytic pathways. TNF-α in blood serum is increased in patients with burns, in patients with sepsis its level is higher. A decrease of the level of TNF-α in BS is associated with the improvement of the condition of patients with burns and sepsis, indicating the potential prognostic significance of TNF-α in this case[66]. Quantitative determination of TNF-α in the study is carried out using enzyme-linked immunosorbent assay[67].

Interleukin-1 (IL-1) is one of the first discovered cytokines, a regulator of inflammatory and immune processes. This protein is encoded by the gene of the same name, located in humans on the short arm of the second chromosome. The length of the polypeptide chain of this protein is 269 amino acids, and the molecular weight is 30.748 Da. It is involved in such biological processes as the inflammatory response and polymorphism. It is localized in the cytoplasm, lysosome, and also secreted to the outside. It is synthesized by many cells of the body, primarily activated macrophages, keratinocytes, stimulated B-lymphocytes and fibroblasts. IL-1 has a wide range of functions in the immune system: they initiate and regulate immune processes, participate in the development of acute and chronic inflammation, and bone tissue resorption. The IL-1 family includes 3 homologous proteins: IL-1α and IL-1β, which are pro-inflammatory proteins, and IL-1RN (IL-1 receptor antagonist), whose molecule has an anti-inflammatory effect. IL-1β plays an important role in the development of both local and systemic inflammatory processes. The hyperproduction of this biomarker at the local level leads, for example, to the destruction of bone tissue in patients with rheumatoid arthritis, and at the systemic level, it leads to catastrophic disruption of hemodynamics and often to death. Content promotion of IL-1β is indicated for exacerbation of pancreatitis, peptic ulcer disease, viral hepatitis, Crohn's disease, pneumoconiosis, and tuberculosis. IL-1β increases chemotaxis, phagocytosis, hematopoiesis, vascular wall permeability, cytotoxic and bactericidal activity, exhibits a pyrogenic effect, and also triggers reactions of the inflammatory-regulatory cascade, stimulates collagen synthesis. The increased level of IL-1β is determined in the synovial fluid of patients with rheumatoid arthritis and in the cerebrospinal fluid of patients after neurological inflammation or strokes.

[66] Arslan E., Yavuz M., Dalay C. The relationship between tumor necrosis factor (TNF)-alpha and survival following granulocyte-colony stimulating factor (G-CSF) administration in burn sepsis. Burns 2000; 26:521–4. [DOI: 10.1016/s0305-4179(00)00024-3] [Cited by in Crossref: 15] [Cited by in F6Publishing: 8] [Article Influence: 0.7] [Reference Citation Analysis].

[67] Pipa L. V. The diagnostic value of modern biomarkers of the development of purulent-bacterial diseases in children L. V. Pypa, M. M. Murgina, R. V. Svistlynyk JOURNAL "ACTUAL INFECTOLOGY". VOLUME 6, № 1, 2018. P. 63–65. doi: http://dx.doi.org/10.22141/2312-413x.6.1.2018.125634

Monitoring the content of this biomarker in the blood is a non-invasive and accessible research method that allows to assess the degree of activity of the inflammatory process[68].

Interleukin-6 (IL-6) is a protein encoded by the gene of the same name, located in humans on the short arm of the seventh chromosome. The length of the polypeptide chain of this protein is 212 amino acids, and its molecular weight is 23.718 Da. The protein coded by the gene belongs to cytokines, growth factors and phosphoproteins by function. It is also involved in such a biological process as the acute phase of inflammation, secreted to the outside. It is a pleiotropic cytokine that is produced in leukocytes, liver, spleen, kidneys and is induced in a number of other cells. IL-6 has a wide range of immune functions, including acute-phase response, induction of fever, simulation of stress hormone production, hematopoiesis and also promotes maturation and activation of immune cells. A rather high level of IL-6 is observed in burn patients with sepsis. This biomarker has been identified as a potential predictor of mortality in burn patients and correlates with the area of a burn wound. The utility of IL-6 as a biomarker of sepsis in patients with trauma has recently been analyzed. It was found to have the same diagnostic value as PCT with relatively high specificity (78 %) and low sensitivity (68 %). These results confirm the possibility of using IL-6 as a validated test for the diagnosis of sepsis.

The rational management of the early postoperative period is fundamentally important in surgeons' clinical practice. The most important points are the prevention of infectious and inflammatory complications and the prevention of EI syndrome. IL-1, IL-6 and other cytokines are also sensitive markers of infectious endotoxicosis and systemic inflammatory reaction. The determination of IL-6 is now already used for daily monitoring of the above criteria. An increase in the concentration of IL-6 to 15–80 mg/l per day precedes the appearance of fever and other clinical symptoms of systemic inflammation. The IL-6 level of above 150 mg/L usually indicates the presence of sepsis. At the same time, in patients with gram-positive sepsis, the level of IL-6 reaches 400–500 mg/l, and in gram-negative – 2000 mg/l or more.

Interleukin-8 (IL-8) is a protein encoded by the gene of the same name, located in humans on the short arm of the fourth chromosome. The length of the polypeptide chain of the protein is 99 amino acids, and the molecular weight is 11.098 Da. The protein coded by the gene belongs to cytokines. It is involved in such biological processes as inflammatory response,

[68] Mizutani H. Rapid and specific conversion of precursor interleukin 1 beta (IL-1 beta) to an active IL-1 species by human mast cell chymase / H. Mizutani 1, N. Schechter, G. Lazarus, R. A. Black, T. S. Kupper. 1991 Oct 1; 174(4):821–5. doi: 10.1084/jem.174.4.821

chemotaxis, secreted externally. IL-8 is a proinflammatory cytokine produced by macrophages, monocytes, and endothelial cells[69]. This biomarker contributes significantly to the activation and migration of neutrophils, promoting chemotaxis. The potential utility of IL-8 as a predictor of sepsis in burn patients was first reported in 1995. In the paper[70], the authors studied the expression profile of 17 different cytokines in 468 children with severe burns and divided the patients into two groups based on the obtained results regarding the level of IL-8 (threshold value 2,34 ngram/ml). A number of authors found that patients with an elevated level of IL-8 (>2,34 ngram/ml) septic complications developed.

Interleukin-10 (IL-10) is an anti-inflammatory cytokine, a product of the human IL-10 gene. Signal transmission mediated by IL-10 is ensured by a receptor complex consisting of two IL10RA (alpha-subunits) and two IL10RB (beta-subunits). This biomarker activates the STAT3-mediated signaling pathway. The phosphorylation of receptors takes place under the action of JAK1 and Tyk2 kinases for alpha and beta subunits. IL-10 is a dimeric protein, each subunit consists of 178 amino acids[71]. It belongs to the second class of cytokines along with interleukins 19, 20, 22, 24, 26 and interferons of the first type (alpha, beta, epsilon, kappa and omega), the second type (gamma) and the third type (lambda, or interleukins 28 and 29). IL-10 has multiple pleiotropic effects on immunoregulation and inflammation. It reduces the expression of Th1 cytokines, MHC class II antigens and co-stimulatory molecules on macrophages. It increases the survival of B-cells, their proliferation and the production of antibodies.

After the discovery of IL-10 in 1991, it was found initially to inhibit cytokine synthesis, antigen presentation, and CD4+ T-cell activation. It was later shown to inhibit lipopolysaccharide and other bacterial products-mediated induction of the secretion of the inflammatory cytokines. IL-10 is an anti-inflammatory cytokine that regulates the proliferation and activation of immune cells, such as macrophages, B-cells, Th1 and NK-cells[72]. This biomarker promotes the production of pro-inflammatory cytokines IL-2,

[69] Baggiolini M., Clark-Lewis I. Interleukin-8, a chemotactic and inflammatory cytokine. FEBS Lett. 1992; 307 (1):97–101.

[70] Kraft R., Herndon D.N., Finnerty C.C., Cox R.A., Song J., Jeschke M.G. Predictive value of IL-8 for sepsis and severe infections after burn injury: a clinical study. Shock. 2015; 43 (3):222–227.

[71] Zdanov A., Schalk-Hihi C., Gustchina A., Tsang M., Weatherbee J., Wlodawer A. Crystal structure of interleukin-10 reveals the functional dimer with an unexpected topological similarity to interferon gamma (англ.) // Structure : journal. – 1995. – June (vol. 3, no. 6). – P. 591–601. – doi: 10.1016/S0969-2126(01)00193-9 – PMID 8590020.

[72] Asadullah K., Sterry W., Volk H. D. Interleukin-10 therapy-review of a new approach. Pharmacol Rev. 2003; 55 (2):241–269. – PubMed.

IL-3, IL-4 and TNF-α[73]. The level of IL-10 anti-inflammatory response levels are elevated in patients with sepsis. The level of IL-10 in BS increases after a burn injury and gradually decreases during recovery.

Interleukin-12 (IL-12) is a heterodimeric cytokine with a molecular weight of 70 kDa, consisting of two covalently linked glycosylated chains with a molecular weight of 40 kDa (p40) and 35 kDa (p35). IL-12 is mainly produced by monocytes, macrophages, and dendritic cells in response to bacterial products such as LPS, intracellular pathogens, or interaction with activated T cells. IL-12 was originally discovered for its ability to induce interferon-gamma (IFN-γ) cell proliferation and cytotoxicity mediated by natural killer cells and T cells production. IL-12 was originally discovered for its ability to induce interferon-gamma (IFN-γ) cell proliferation and cytotoxicity mediated by natural killer cells and T cells.

Presepsin (PSP) was discovered in Japan in 2005 and indicates the development of a generalized bacterial infection in the patient's body. It has been verified as an early identifier of sepsis, and presepsin levels in BS are closely related to the severity of sepsis. Presepsin (sCD14-ST) is a humoral protein with a molecular weight of 13 kDa, specific for phagocytosis, which is formed as a result of a cascade of reactions with mCD14, a membrane receptor of macrophages, upon binding of bacteria by the TLR4 receptor. The level of presepsin is a highly specific early biomarker of sepsis caused by both gram-positive and gram-negative microflora and fungi. An increase in the level of PSP is not observed in patients with viral infections. It can be used both for diagnosis and for monitoring the condition and effectiveness of sepsis therapy. The quantitative determination of presepsin was carried out as part of the study on the Pathfast automatic chemiluminescent enzyme immunoassay using Pathfast Presepsin (LSI Medience Corporation).

The authors of the paper[74] established the limit value of presepsin as a prognostic tool for the mortality of patients in a critical condition with sepsis. Only one of the studies evaluated the possible role of presepsin in burn patients who developed sepsis and expressed the opinion about its relatively high diagnostic accuracy, close to that when using PCT. It is important to note that an increase of the level of presepsin was observed earlier than in the case of PCT, leukocytes and CRP by 1 day. Procalcitonin and presepsin are currently reliable diagnostic markers of bacterial inflammation, but presepsin is the most specific and sensitive biomarker and can be used for differential diagnosis of localized and bacterial process and sepsis.

[73] Kumar S., Shukla R., Ranjan P., Kumar A. Interleukin-10: a compelling therapeutic target in patients with irritable bowel syndrome. Clin Ther. 2017; 39 (3):632–643.

[74] Zhang J., Hu Z.-D., Song J., Shao J. Diagnostic value of presepsin for sepsis: a systematic review and meta-analysis. Medicine (Baltimore). 2015; 94 (47):e2158.

Lactate. Well-known laboratory tests help doctors to assess whether the clinical condition of patients changes during the transition from sepsis to severe sepsis. The most widely used biomarker that can provide information about the impact on organ dysfunction is the blood lactate level. It is known that glucose is metabolized to pyruvate anaerobically and in most tissues pyruvate is further oxidized in mitochondria. However, in the case of absence of a sufficient amount of oxygen, mitochondrial metabolism is disturbed. When this occurs, cells form lactate from pyruvate in order to regenerate the cofactor nicotinamide adenine dinucleotide (NAD) to continue upstream anaerobic glycolysis.

However, there are other explanations of the increase in the lactate levels in patients with sepsis. Lactate is produced constantly by erythrocytes that lack mitochondria, as well as by some tissues with a high rate of glycolysis, even if tissue perfusion is not impaired. The liver converts most of this lactate into glucose and oxidizes the rest. At the same time, liver dysfunction is associated with sepsis, which can lead to impaired lactate clearance[75]. Systemic inflammation can also lead to the increased anaerobic glycolysis, as the increased rate of glucose metabolism in damaged tissues often exceeds the oxidative capacity of mitochondria. A recent comparison of patients with septic shock with and without elevated lactate seems to support the idea that there may be other factors responsible for lactate synthesis in patients with sepsis.

Platelet-activating factor (PAF) is a potent pro-inflammatory biomarker that exhibits a distinct spectrum of biological and pharmacological effects. PAF was discovered in the early 1970s by the French immunologist Jacques Benveniste, and in 1979, Konstantinos Demopoulos established the structure of this compound. This is a strong phospholipid mediator of inflammation. It is synthesized by many types of cells: neutrophils, basophils, platelets and endothelial cells. Participates in inflammation, aggregation of platelets, plays a role in the pathogenesis of anaphylactic shock. Importantly, it is involved in a wide range of pathophysiological conditions. In the cardiovascular system, PAF has been shown to play an important role in platelet and neutrophil aggregation, vascular permeability, microvascular leakage, thrombus formation, leukocyte adhesion to endothelial cells, and the initiation and progression of atherosclerosis. Detailed information about PAF, a family of lipids is associated with the pathology of coronary heart disease due to their association with leading etiological mechanisms such as inflammation, endothelial dysfunction, oxidative and nitrosative stress, and platelet

[75] Mikkelsen M. E., Miltiades A. N., Gaieski D. F., et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure or shock. Crit Care Med. 2009; 37:1670–7. – PubMed.

reactivity, is presented. This review further provides information about PAF and its potential role as a key factor in the pathogenesis of cardiovascular disorders. The detailed information about PAF is presented in[76].

Human leukocyte antigen (HLA system) is an important part of the human immune system, which is controlled by the genes located on the sixth chromosome. The HLA complex is the human version of a complex found in many animals and has a more general name MHC "major histocompatibility complex". These genes encode molecules located on the cell surface and present parts of proteins for recognition by T-cell receptors[77]. The HLA complex is known for its significant role in organ transplantation. In order to reduce the risk of organ rejection, the donor and the recipient were selected according to the principle of the best compatibility between their HLA genes. Variations in HLA genes are associated with many diseases, including infectious diseases, autoimmune diseases, and some types of cancer.

Clinical studies have focused on monocyte expression of HLA-DR, which was suppressed markedly in most patients with sepsis initially, but recovered within ten days in surviving patients. Similar depression may occur after severe trauma, and the lack of recovery during the first week of hospital stay in surviving patients is a real predictor of developing sepsis in these patients. Low expression levels of HLA-DR expression predict a low percentage of patient survival, as well as an increased risk of nosocomial infection. The clinical utility of measuring IL-10, which suppresses MHC class II expression, and TGF-β costimulatory molecules, which suppresses T-cell proliferation, has been demonstrated. Elevated levels of IL-10 predict mortality in patients with severe sepsis. It was also established that they correlate with inhibition of HLA-DR monocyte expression. It was also noted that IL-10 was a reliable biomarker of neonatal sepsis. It was also shown that in the case of the early and late-onset sepsis, a rather rapid increase in the level of IL-10 after the onset of the disease was practically not observed. TDF-β has been shown to promote tissue repair, but its role is not as beneficial as that of IL-10.

CD28 molecule is a protein encoded by the gene of the same name, located in humans on the short arm of the second chromosome. The length of the polypeptide chain of the protein is 220 amino acids, and the molecular weight is 25.066. The protein coded by the gene belongs to phosphoproteins

[76] Anand Vijaya Kumar Palur Ramakrishnan, Treesa P. Varghese, Sreedevi Vanapalli et el. Platelet activating factor: A potential biomarker in acute coronary syndrome? Cardiovasc Ther. 2017 Feb; 35 (1):64–70. doi: 10.1111/1755-5922.12233

[77] Cheron A., Floccard B., Allaouchiche B., et al. Lack of recovery in monocyte human leukocyte antigen-DR expression is independently associated with the development of sepsis after trauma. Crit Care. 2010; 14:R208. – PMC. – PubMed.

by function. Involved in such a biological process as alternative splicing. It is localized in the membrane.

Transforming Growth Factor beta, TGFβ, is a systemic cytokine that affects directly or indirectly, apparently, all processes in the human body. The most studied and important is TGFβ-1[78], which plays one of the main roles in the regulation of the immune system (this biomarker is usually released by suppressor cells and suppresses the activation of the immune system). TGFβ-1 is one of the main regulators of carcinogenesis. It was also shown that TGFβ-1 inhibits the growth and division of normal human cells, but enhances the growth and migration of highly transformed cancer cells. At high concentrations, TGFβ-1 can even cause the death of normal human cells (mainly by apoptosis and especially in cells of the immune system).

The primary model of sepsis is the immune response to endotoxin, LPS, which has been found in the cell walls of gram-negative bacteria. Endotoxin is an example of the pathogen-associated molecular pattern (PAMP). 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. It is these pro-inflammatory cytokines that cause the systemic inflammatory response. For a long time, doctors believed that sepsis was an overreaction of the innate immune system to a bacterial infection. The consensus conference of 1991 defined "sepsis" as a combination of infection with two or more signs that SIRS was realized.

Roger C. Bone evaluated sepsis to be more than severe hyperinflammatory SIRS[79]. The importance of CARS (compensatory anti-inflammatory response syndrome)[80], which often follows the hyperinflammatory phase, has also been emphasized, especially in patients who develop severe sepsis. In patients with severe sepsis there are also signs of severe organ dysfunction. This may

include lung, liver and/or kidney damage, as well as cognitive impairment. The terminal stage of severe sepsis is the septic shock, in which patients develop cardiovascular collapse and often do not respond to infusional vasopressor therapy. Thus, two phases can be distinguished in the dynamics of sepsis. During this phase, signs of CARS with immunosuppression and multiple organ dysfunction appear. At this stage, it

[78] Blobe G. C., Schiemann W. P., Lodish H. F. (May 2000). Role of transforming growth factor beta in human disease. *N. Engl. J. Med.* 342 (18): 1350–8. PMID 10793168. doi:10.1056/NEJM200005043421807

[79] Balk R., Roger C. Bone, M. D. and the evolving paradigms of sepsis. Contrib Microbiol. 2011; 17:1–11. – PubMed.

[80] Bone R. C., Grodzin C. J., Balk R. A. Sepsis: a new hypothesis for pathogenesis of the disease process. Chest. 1997; 112:235–43. – PubMed.

is fundamentally important to carry out effective treatment, otherwise exitus lethalis will take place.

As the sepsis paradigm has evolved over time, and various therapeutic approaches to sepsis have been tested, various approaches, including various biomarkers, have been used to the diagnostics and treatment of sepsis. Initially, the main focus, starting in 1980, was on the early hyperproinflammatory phase with the use of high-dose corticosteroids, which were an important component of its treatment. Further research and progress in solving the main problems of sepsis were closely related to the use of pro-inflammatory cytokines, in particular TNF-α, IL-1β та IL-6, which cause SIRS and CRP appear, the synthesis of which in the liver is activated by 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 diagnostics and treatment of septic complications. Recently, when the therapy was aimed at the anti-inflammatory phase of sepsis, new scientific research began and new biomarkers were studied. After recognizing the importance of CARS biomarkers of the immunosuppressive phase of sepsis deserve considerable attention. There is 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 a 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.

Clinical studies were focused on monocyte HLA-DR expression, which was rather suppressed in most patients with sepsis initially, but recovered within ten days in surviving patients[81]. Similar depression may occur after a severe trauma, and failure to recover within the first week of hospital stay in surviving patients is a real predictor of developing sepsis in these patients[82]. Low levels of HLA-DR expression predict low percentage of patient survival, as well as an increased risk of nosocomial infection[83, 84].

[81] Tschaikowsky K., Hedwig-Geissing M., Schiele A., et al. Coincidence of pro- and anti-inflammatory responses in the early phase of sepsis: longitudinal study of mononuclear histocompatibility leukocyte antigen-DR expression, procalcitonin, C-reactive protein, and changes in T-cell subsets in septic and postoperative patients. Crit Care Med 2002; 30:1015–23 [Google Scholar].

[82] Cheron A., Floccard B., Allaouchiche B., et al. Lack of recovery in monocyte human leukocyte antigen-DR expression is independently associated with the development of sepsis after trauma. Crit Care 2010; 14:R208 [Google Scholar].

[83] Monneret G., Lepape A., Voirin N., et al. Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock. Intensive Care Med 2006; 32:1175–83 [Crossref], [PubMed], [Web of Science®], [Google Scholar].

Clinical utility of measuring IL-10, which inhibits the expression of MHC class II and costimulatory molecules of TGF-β, which suppresses the proliferation of T cells, has been proven. Elevated levels of IL-10 predict mortality in patients with severe sepsis. It was also established that they correlate with inhibition of HLA-DR monocyte expression[85]. In[86] it was noted that IL-10 is the reliable biomarker of neonatal sepsis. It was also shown that at early and late onset of sepsis, a fairly rapid increase of the level of IL-10 was practically not noticed [87]. It was also shown, that TGF-β promotes tissue repair, but its role is not as important as IL-10.

None of the biomarkers discussed in the above publications are perfect, but in principle, they can be useful. In order to more deeply study of the change in the health status of patients during the treatment 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 have the most global impact on the change of the health status of patients. Over the time, a lot of attention is paid to the search for new biomarkers of septic complications. Nonetheless, the problem mentioned above is not given due attention to. Unfortunately, until now, a biomarker, which meets all the requirements, has not been identified yet.

3. Study of spectral-fluorescence characteristics of blood serum in patients with sepsis, acute inflammatory abdominal pathology and burn injury

The tactics of previous studies about sepsis were directed at the detailed external assessment of the visual state of the body, close to septic. When conducting a biochemical blood analysis for determining protein fractions and albumin level, it was impossible to detect real changes in its structure in patients with purulent-septic complications. So, in order to clarify these changes at the molecular level, it was advisable to analyze the changes of the structure of BS in details in patients with these diseases. In this regard, it was

[84] Landelle C., Lepape A., Voirin N., et al. Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock. Intensive Care Med 2010; 36:1810–2 [Google Scholar].

[85] Monneret G., Finck M. E., Venet F., et al. The anti-inflammatory response dominates after septic shock: association of low monocyte HLA-DR expression and high interleukin-10 concentration. Immunol Lett 2004; 95:193–8 [Crossref], [PubMed], [Web of Science®], [Google Scholar].

[86] Urbonas V., Eidukaite A., Tamuliene I. Increased interleukin-10 levels correlate with bacteremia and sepsis in febrile neutropenia pediatric oncology patients. Cytokine 2012; 57:313–5 [Google Scholar].

[87] Zeitoun A. A. H., Gad S. S., Attia F. M., et al. Evaluation of neutrophilic CD64, interleukin 10 and procalcitonin as diagnostic markers of early- and late-onset neonatal sepsis. Scand J Infect Dis 2010; 42:299–305 [Taylor & Francis Online], [Google Scholar].

very important to develop the new pathogenetic concept in order to improve the diagnostic and treatment model of purulent-septic diseases.

Human serum albumin (HSA) is globular protein. It belongs to the multigene family of proteins, which includes α-fetoprotein, the group-specific component, vitamin D-binding protein and albumin. Serum albumin synthesizes in the liver. During 24 hours, the human body synthesizes 10–15 g of albumin. Its concentration in the blood plasma is 35–50 g/l, in the lymphatic system – 15–36 g/l, in the intercellular fluid – 3 g/l, in the cerebrospinal fluid – 0.3 g/l. The mass of albumin is 66439 Da. It forms 47–62 % of all blood plasma proteins. HSA performs an important function (about 80 %) in maintaining oncotic pressure, is a component of the body's antioxidant defense, and is a source of functionally active oligopeptides that are formed during its degradation in tissues. However, the main function of albumin in the body is the feedback and transport of low molecular weight endogenous and exogenous ligands. Medicines, metabolites (in particular, fatty acids (FA) and heme derivatives), hormones, metal ions and dyes can also bind to albumin. The exact number of ligands, which one molecule of albumin can bind, is not known reliably; sometimes it exceeds ten ligands. Since the degree of center filling is not the same in each of the albumin molecules, there are practically different albumin molecules in the blood plasma in terms of physico-chemical relations. Thus, albumin is a polydisperse protein, even if all its molecules without ligands are exactly the same. An albumin molecule can bind 6 or more FA molecules. The polydispersity (heterogeneity) of albumin depends on the physiological state of the body and is proportional directly to the concentration of FA.

Long-term clinical studies of the level of HSA have proven its important diagnostic value for assessing the severity of the patient's condition and the prognosis of the course of the disease. The basis of this is the ability of albumin to form complexes with toxins, which provide its detoxification function and are important especially for detecting of pathology[88]. At the same time, the reverse side of the sorption of toxins on albumin is the change in its structural state and blocking of binding centers, which leads to the suppression of the transport function of the protein. It has also been proven that in the case of endogenous intoxication (EI) syndrome, which is caused by the release of toxins from the local pathological focus and occurs as the result of pathological processes in various diseases, the binding capacity of albumin in relation to physiological ligands and drugs decreases.

Very valuable information about indicators, which testify to the intensity of all processes of homeostasis in the body, can be obtained by studying the

[88] Serum albumin in clinical medicine / Ed. Yu. A. Gryzunova and G. E. Dobretsova. – M. : GEOTAR, 1998. – 440 p.

state of albumin molecules in the BS. That is why in the recent years, a lot of attention has been paid to the problem of changes in blood of albumin molecules in the case of presence of EI. In the case of severe EI in patients with purulent-septic diseases, conditions in the body are created for the formation of forms of albumin with changed physical and chemical characteristics. It is important to study the functional activity of albumin. In this regard, it is promising to use the method of fluorescent probes to evaluate the features of binding centers of albumin. It makes possible to estimate the effective albumin concentration (EAC) and the total albumin concentration (TAC). At the same time, EAC gives, in fact, information about the amount of full-fledged albumin in BS, which has a normal binding capacity, while TAC is the total concentration of albumin in BS. In patients with purulent-septic diseases the binding capacity of albumin is reduced, which limits the flow of toxic products to the detoxification organs and deepens EI. A decrease in EAC, EAC/TAC indicators are prognostically unfavorable signs. A decrease of the level of complete albumin in the patient's blood is noted usually in the case of presence of a severe infection. In the case of the development of a serious infectious disease in the body, there is an increase of the number of albumin molecules blocked by toxins. This leads to a violation of transport and detoxification functions of the patient's body. An important is the method of assessing the degree of EI by the determination of EAC and TAC.

The immune system is directed to protect the body from toxic compounds. But it ensures the elimination of only high-molecular foreign substances with a molecular weight of at least 5000 Da, and no immune response is produced to low-molecular compounds. The elimination of low molecular weight toxins is provided by another protective system: blood transport proteins (albumin, low density lipoproteins and α-1-acid glycoprotein or orosomucoid), which absorb efficiently both toxins and other low molecular weight ligands. Serum albumin plays a central role in this process, as it has a unique ability to bind a large number of ligands with different structures, including endogenous metabolites, hormones and drugs. The binding process is stereospecific, reversible and ensures the directed transport of toxins into tissues, where their irreversible inactivation occurs. Thus, the effectiveness of the body's protection against low molecular weight toxins can be assessed by the ability of albumin to bind ligands.

Nonetheless, the fluorescent method has the greatest diagnostic value for assessing the degree of severity of surgical patients with purulent-inflammatory diseases and sepsis, including in the postoperative period, since standard quantitative methods of assessing the severity of EI are not correct completely, as they determine the level of toxemia, and not the degree of accumulation of toxins in the blood. Especially important is the

possibility of an early (on the first day after surgery) prognosis of the condition of patients when using fluorescent indicators, which, together with the age of the patients, is at least 85 %. None of the investigated biochemical indicators showed informativeness on the first day after surgery.

The main task of this section is to study the expediency and effectiveness of using of method of fluorescent spectroscopy (MFS) as an express highly sensitive method of diagnosis, especially early, of sepsis and purulent-inflammatory diseases. For this aim, the fluorescence spectra (FS) and fluorescence excitation spectra (FES) of BS of donors, patients with sepsis and patients with purulent-inflammatory diseases and patients with burn injuries were investigated.

In order to carry out the proper assessment and adequate interpretation of the obtained experimental data for the spectral-fluorescence characteristics of BS of patients with various diseases, including the dynamics during the treatment, we proposed and carried out a series of studies of "in vitro" dilutions of BS with distilled water (DW), 20 % donor albumin, sugar broth (SB) and centrifuged and non-centrifuged (CC and NCC) cultures of bacteria.[89, 90] This approach made it possible to study properly the possible changes of the spectral-fluorescence characteristics of patients' BS with various diseases and treatment measures. The detected effect of changes in the spectral-fluorescence characteristics of dilutions of BS with CC and NCC cultures of bacteria are specific and form the basis for the introduction of the fluorescent method for the early diagnosis of sepsis by studying the spectral-fluorescence models of sepsis in vivo. The task set in our research is qualitatively different from the approach used in this paper[91]. This made it possible to study properly the possible changes of the spectral-fluorescence characteristics of patients' BS with various diseases and treatment measures. The detected effect of changes in the spectral-fluorescence characteristics of dilutions of BS of NCC and bacterial CC have a specific nature and form the basis for the introduction of a fluorescent method for the early diagnosis of sepsis by studying the spectral-fluorescence models of sepsis in vivo.

The authors of the papers, which are presented and discussed in the above research, focus on the search for the specific spectral-fluorescent physiological parameters of the body that are changed quantitatively in

[89] Modeling of blood serum changes in patients with various diseases and treatment measures / O. V. Bulavenko, I. D. Gerych, L. R. Ostapiuk [et al.] // Biomedical and biosocial anthropology. – 2013. – Vol. 20. – P. 8–14.

[90] Luminescent-spectral model of sepsis in vitro / I. D. Gerych, L. R. Levitska, A. S. Voloshinovskii, S. V. Myagkota // Mat. of science conf. "Actual issues of abdominal and purulent-septic surgery". – Lviv, 2004. – P. 111–112.

[91] Chernytskyi E. A. Spectral luminescent analysis in medicine / E. A. Chernytskyi, E. Y. Slobozhanina. – Minsk : Science and Technology, 1989. – 141 p.

patients with various pathologies, while we concentrate on the detection of spectral-fluorescent signs pathognomonic for sepsis of pathological constellation of "blood serum bacteria", i. e. the phenomenon of bacteremia.

We conducted the research in two stages. At the first stage, we studied the BS of 50 patients with purulent-inflammatory diseases and sepsis who were treated during 2001–2008 and 40 people of the control group. Among the patients there were 15 patients with sepsis and 35 people with acute inflammatory abdominal pathology, who obtained inpatient treatment at the Emergency Hospital in Lviv. At the second stage, the main group of the study consisted of 20 patients with burn injuries who obtained inpatient treatment in the burn department of the "Saint Luke Hospital" in Lviv during 2015–2018. The detected changes of the spectral-fluorescence characteristics of the BS of patients in most cases had a pre-manifest nature: usually they were recorded 24–48 hours before the appearance of obvious clinical and laboratory signs of a significant change in the general somatic status of patients[92]. At the same time, the structure of the FES of donors and patients with purulent-inflammatory diseases is qualitatively similar in general, but the intensity of excitation spectra in patients is significantly lower than in donors. FS of BS of patients and individuals of the control group was studied when BS samples were excited by light in the region $250 \le \lambda_{ex} \le 280$ nm. Contours of radiation bands when the wavelength changes λ_{ex} excitation light practically did not differ from each other.

At the first stage of our research within the framework of the MFS, insufficient attention was paid to the in-depth understanding of the pathological processes that occur in the bodies of patients with various diseases at the molecular level and are recorded within the framework of the MFS. During the further research, we carried out a detailed analysis and generalization of previous results, as well as created a qualitatively new concept and interpretation of experimental results obtained within the framework of MFS. We proposed the **pathogenetic concept of diagnostic and treatment model of purulent-inflammatory diseases** and sepsis. It is based on the fact that albumin molecules in the blood of people have the ability to complex. In the diseases which are accompanied by EI, 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

[92] Pat. № 76953 Ukraine A61B 17/00 G01N 33/48, G01N 21/64 Method of early diagnosis of purulent-septic complications using the method of fluorescence spectroscopy / I. D. Gerych, O. V. Bulavenko, L. R. Ostapyuk, A. S. Voloshinovsky, S. V. Myagkota, applicant and patent holder Vinnytsia National Medical University. – № 201207441; statement 19.06.2012; published 25.01.2013, Bull. № 2.

functions, namely transport and detoxification. We explored the specific features of the origin and course of purulent-septic processes in the patients' bodies until their recovery. **The proposed diagnostics 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. If $X \rightarrow X^*$ the health of patients deteriorates and they may go into a septic state. When the condition of patients worsens, the possibility of endogenous albumin synthesis in their bodies significantly decreases. In this regard, in order to prevent the reduction of X, there is a need for infusion of exogenous albumin solutions for patients in a critical condition to support properly the vital activity of the body. In the course of treatment, the amount of toxins in the blood of patients decreases gradually. This makes it possible to cancel infusions of donor albumin solutions at a certain time, since the synthesis of endogenous albumin in the liver in the patient's body gradually normalizes.

Before moving on to the discussion of the results of the BS study of patients with purulent-septic complications obtained by us within the framework of the MFS, let's dwell in more detail on the main idea of the pathogenetic concept of the diagnostic-treatment model of purulent-inflammatory diseases and sepsis. We have already noted that in diseases accompanied by EI, there are normal and pathological albumin molecules in the blood of patients. Although the total concentration of albumin in the body can be within the normal range, its real "effective" concentration can be significantly reduced. The determination of the "effective" concentration of albumin cannot be carried out by the modern generally accepted diagnostic methods, which are currently widely used in the laboratories of health care institutions. Taking into account the pathogenetic changes of albumin molecules in EI, an important point of pathogenetic treatment, as we noted above, is the use of albumin solution infusions in the complex therapy. At the same time, the infusion of exogenous albumin solutions worsens the synthesis of endogenous albumin in the human body. However, without this infusion, in the case of presence of severe EI, the body will not be able to overcome it on its own[93].

We proposed to use MFS for the diagnosis, monitoring and correction of the treatment process. The main characteristics which we investigate within the MFS for the BS of patients with purulent-septic complications are I_F and

[93] Ostapiuk L. R. Forming students' skills of assessing the prognosis of posrpartum purulent-inflammatory diseases / Innovative methods for the organization of educational process for medical students in Ukraine and EU countries // LR. Ostapiuk. Cuiavian University in Wloclawek, scientific and pedagogic internship. – August, 3 – September, 11, 2020. – Wloclawek. Republic of Poland. – P. 83–88.

λ_{max}. They depend on X and are determined by the following interpolation ratios for a mixture of normal and pathological proteins in the BS:

$$I(X) = I^{a}_{f} * X + I^{t}_{f} * (1 - X)$$

$$\lambda_{max}(X) = \lambda^{a}_{max} * X + \lambda^{m}_{max} * (1 - X)$$

They describe the corresponding characteristics for normal (I^{a}_{F}, λ^{a}_{max}) and pathological (I^{t}_{F}, λ^{t}_{max}) albumin molecules.

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.

We will dwell on the most important and interesting of them. The introduction of new methods of diagnosis and treatment have always been the driving force of progress in medicine. In order to make such searches successful, a scientific approach, a clear formulation of the task and painstaking work were needed. To assess the possibilities of using MFS in medical practice, as mentioned above, a series of "in vitro disease model" experiments was performed. As a result of a thorough analysis of the results obtained in this case, clear trends of changes of the spectral-fluorescence characteristics of BS were revealed. They can be observed probably in various pathological conditions, including severe ones. In this case, although the patient was admitted to the hospital not at the stage of the formation of the septic state, but against the background of its manifestation, the MFS helped us to identify the septic peak in the long-wave region (Fig. 3.1, curve 1) and to decide on the further rational choice of tactics treatment. The suppression of bacteremia (blood culture from December 28, 2001 – St. aureus) as a result of the treatment process contributed to the reduction of the number of pathological albumin molecules in the patient's blood. In its turn, this contributed to the process of restoring the synthesis of endogenous albumin by the liver.

As a result of an in-depth analysis of the situation described above (growth of X), we modeled scenarios of the behavior of the BS of this patient on December, 30, 2001 and on January, 2 2002 (Fig. 3.1, curve 1' and curve 1''). The right peaks of these curves indicate a gradual decrease in the concentration of pathological albumin molecules, and the left peaks

indicate, respectively, an increase in the concentration of complete albumin in the patient's blood. At the next measurement of FS of BS (Fig. 3.1, curve 2) the intensity of this band, which was $1.07*I^F$, increased significantly and at first glance unexpectedly. In fact, this result was expected. Taking into account the subcompensated changes in the absolute quantitative and qualitative content of proteins in BS at the time of the examination (biochemical studies from January 2–4, 2002: total protein and protein fractions were at the lower limit of normal), the rapid increase in the intensity of the fluorescence band of the patient's BS cannot be interpreted as absolute hypoproteinemia, which typically causes a weakening of the concentration quenching of fluorescence that is characteristic of protein fluorescence. The only possible explanation for the phenomenon of increase in the intensity of the BS fluorescence band of this patient, which we registered above, can be the presence of transient hypervolemia during this period of treatment: the volume of daily intravenous infusions during this period of treatment was 8–10 liters. Under such circumstances, a natural increase in the liquid component of the BS leads to the pseudohypoproteinemia, i. e. a laboratory phenomenon that is not detected by the standard biuret reaction and can be differentiated from true hypoproteinemia only with the help of a special technique and the Phillips and van Slyke normogram. In our opinion, the forced excessive therapeutic dilution of blood during this period became the reason for the weakening of the concentration quenching of the fluorescence of the patient's BS and led to the increase in the intensity of the fluorescence bands of her BS. The above-mentioned significant increase in the intensity of the fluorescence band of her BS from January 4, 2002 was influenced, undoubtly, by the reduction of septic symptoms. Our in vitro studies of the spectral-fluorescence characteristics of standard dilutions of BS with the DW confirmed the correctness of our proposed explanation of the registered phenomenon of increasing intensity of the BS fluorescence band of this patient from January 4, 2002.

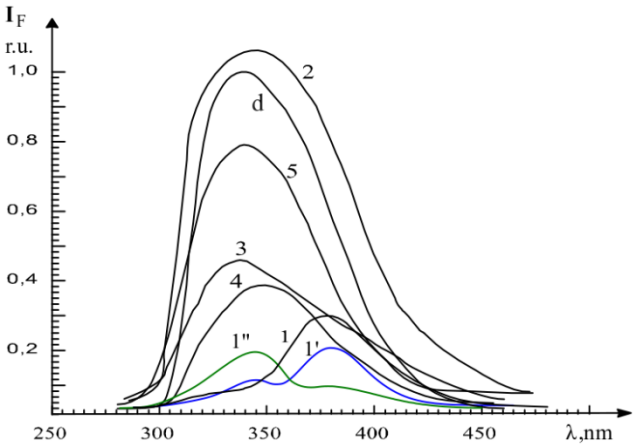

Fig. 3.1.

Fluorescence spectra of blood serum of the patient 1 with sepsis, who was treated at the Emergency Hospital in 2001–2002: 1 – 28.12.2001; 1 '– 30.12.2001, 1''– 02.01.2002; 2 – 04.01.2002; 3 – 12.02.2002; 4 – 19.03.2002; 5 – 04.06.2002 and blood serum of the donor (d) λex = 250 nm (340 nm – "normal peak", 380 nm – "septic peak").

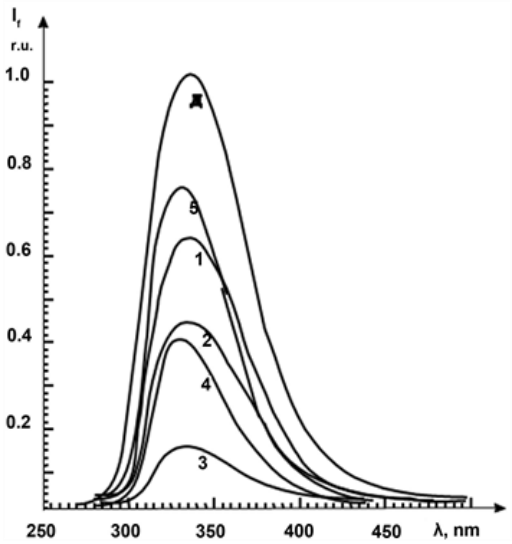

Fig. 3.2.

Fluorescence spectra of the blood serum of the patient 2 with sepsis-epiduritis, who was treated in 2002 at the 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.

Table 1

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

N	d	1	1’	1’	1’’	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
λ_{max} **nm**	340	380	380	345	380	345	345	337	349	340
I^F, **r.u.**	1,0	0,3	0,21	0,12	0,09	0,2	1,07	0,46	0,39	0,79

Table 2

Changes in the spectral-fluorescent characteristics of the serum of a patient 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

Further studies of the FS of BS of this patient (see Fig. 3.1, curves 3, 4) proved that the bacteremia in her body was not overcome completely, though the long-wave septic peak disappeared. Currently, the competition between bacteremia and the compensatory capabilities of her body in combination with complex medical measures has been going on. At the time of treatment of this patient, a pathogenetic model had not been proposed yet and infusion therapy with solutions of donor albumin was not prescribed. This could speed up significantly the recovery process of this patient. Only a further long process of treatment under the influence of complex therapy led to the complete suppression of bacteremia and recovery of the patient (Fig. 3.1, curve 5).

The serious condition of the patient after the operation and the lack of the experience did not enabled us to clarify really the nature of the change in the FS of the patient during six days after her operation. “In vitro” studies would enabled us to study the behaviour of FS only at low concentrations of toxins. Only the preparation of concentrated solutions of BS by bacterial culture would give us an opportunity to study in detail within the framework of MFS the process of formation and behaviour of the septic peak at a severe stage of the course of sepsis.

During the treatment of patients with sepsis, it is necessary to examine samples of their BS more often and adjust the treatment process in order to prevent their transition to a state with $X<X^*$. In the following studies of the spectral-fluorescence characteristics in the septic area, infusions of solutions of donor albumin should be used. This approach will make it possible to

reproduce a real picture of the improvement of the behavior of the spectral-fluorescence characteristics during infusions.

Very important 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 the Emergency Hospital in June 2002. For this patient, because of the timely hospitalization and early surgical elimination of the source of infection (blood cultures from June 3–6, 2002 – Kl.pneumoniae), the progress of the septic process was much easier, which was significantly reflected in the dynamics by the changes of spectral-fluorescence characteristics (Fig. 3.2, Table 2).

We present the results of the most likely scenarios of the development of sepsis that we have identified. The comparison of the results of FS of BS research and the typical course of the clinical features of sepsis in the two cases considered above makes it possible to conclude about the similar nature of the recovery dynamics of the mentioned patients in the postoperative period. At the same time, the study of FS of BS of these patients, in contrast to the convection methods of clinical and laboratory assessment of the patient's condition, enables us to follow clearly the nature of the course of the disease and, if necessary, to adjust the appropriate treatment procedures until the patients recover.

Against the background of EI, which occurs with a burn disease, the repair of tissues in the area of inflammation and the restoration of homeostasis are sharply complicated. In this regard, attention should be paid to the problem of a possible complication of a burn disease: sepsis. So, it is necessary to consider deeply and take into account at the molecular level the changes that occur in the bodies of patients with burn injuries. The effective operative treatment of burn surfaces, the timely verification of sources of infection, reliable diagnosis and the proper control of the treatment process within the framework of MFS can ensure adequate treatment of patients with burn injuries. We illustrate the results of two critically ill burn patients treated with our proposed approach. In order to compare the obtained results for the spectral-fluorescence characteristics of BS of patients with burn injury, we will also present the results of the spectral-fluorescence characteristics of the patient with sepsis (Fig. 3.2), who recovered after successful treatment.

Fig. 3.3 presents the results of studies of FS in dynamics of the BS of the patient with a burn injury who was admitted to the hospital on June 27, 2015, the area of the burn surface was 38 %. On the basis of microbiological examination, Staphyloccus aureus 10^5 та Pseudomonas aeruginosa 10^6 were verified in this patient. The patient was prescribed immediately appropriate treatment, including antibiotic and infusion therapy with a volume of 2–3 liters daily. As a result of receiving infusion therapy, the intensity of FS

of BS compared to the intensity of albumin fluorescence (I_F = 1.00) did not decrease significantly for several days (I_F = 0.88), which correlates with the results of the in vitro study.

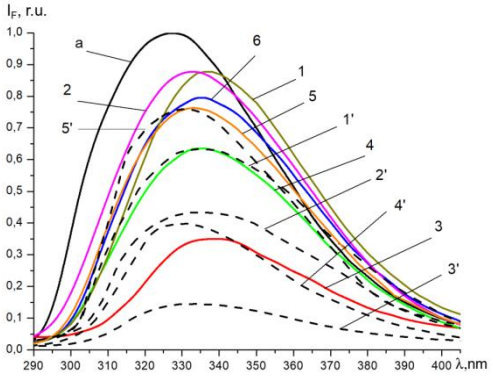

Fig. 3.3.

Fluorescence spectra of blood serum of the patient with a burn injury who was undergoing inpatient treatment in the St Luke Hospital in 2015 in the 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 who was treated in 2002 at Emergency Hospital (1' – 03.06; 2' – 05.06; 3' – 06.06; 4' – 07.06) and 20 % donor albumin (a), λ^{ex} = 280 nm.

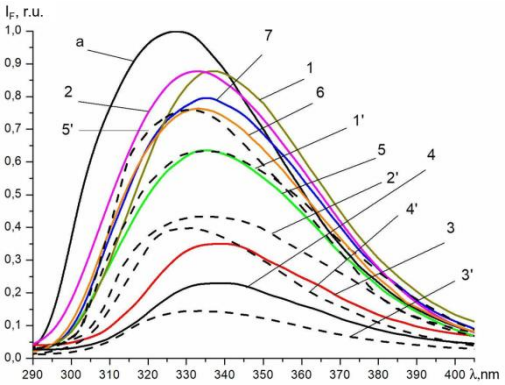

Fig. 3.4.

FS of BS of a patient with a burn injury who was hospitalized in the St Luke Hospital 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 and 20 % donor albumin (a), (a), λ^{ex} = 280 nm.

At the same time, there was also no noticeable shift of FS of BS to the long-wave range, despite the verification of several pathogens. FS of BS

measurements 10 days after the patient was admitted to the hospital on July 13, 2015 (Fig. 3.3, curve 3), testified to the critical moment when there was a significant decrease in I_F to 0.35 r. u. and a shift of FS to the long-wavelength region by 9 nm. This condition of the patient was close to septic (Fig. 3.3, curves 3 and 3'). This was due to the increased bacteremia in this patient. MFS made it possible to detect the worsening of this patient's condition. With the successful organization of the treatment process, including the use of infusions with a 20 % solution of donor albumin, the patient's condition improved and he was discharged from the hospital in the satisfactory condition to continue the treatment at his place of residence. We illustrate the possibilities of the development of a septic state for a patient whose FS are presented in fig. 3.3, which can occur with improper organization of the treatment process.

On fig. 3.4 (curve 3) we can see that on July 13, a decrease of the fluorescence intensity and a long-wave shift of the FS were recorded within the framework of the MFS. If we do not take into account the MFS data on July 13 and do not prescribe an infusion of donor albumin, bacteremia will increase and within the framework of the MFS we will get curve 4 (Fig. 3.4). It can be seen from this figure that the patient's condition has approached septic (curves 4 and 3' are quite close to each other). Because of the monitoring of the treatment process within the framework of the MFS, it is easy to identify a threatening situation for this patient. Thus, he needs several sessions of infusion therapy with a solution of donor albumin until he recovers.

The scenario of his treatment at the final stage took place under the supervision of the MFS and is illustrated in fig. 3.4. If the infusion of donor albumin had not been prescribed on July 17, his health condition against the background of increasing EI could have continued to deteriorate more noticeably.

If we were to study the FS of BS in this case, it could turn out that the corresponding curve could be shifted to the long-wave region, and its intensity could be lower than that for curve 3'. In this case, the treatment with the use of infusion therapy with a solution of donor albumin should also be continued, though there is no guarantee of the successful completion of the treatment process in this case. In case of absence of the possibility of monitoring the treatment process within the framework of the MFS, it is necessary to monitor carefully the condition of patients and to correct in time the treatment process, including timely prescribing of infusion therapy with a solution of donor albumin.

Fig. 3.5 presents the results of research in the dynamics of FS of BS of the another patient with a burn injury (28 % burn surface area), who was hospitalized in February 2017. He was prescribed immediately appropriate

treatment, including antibiotic therapy and infusion therapy with a volume of up to 3 liters daily, as well as infusions of 10 % donor albumin (06.02, 10.02 100 ml each day). The condition of this patient was much worse than that of the patient whose results are presented in fig. 3.3.

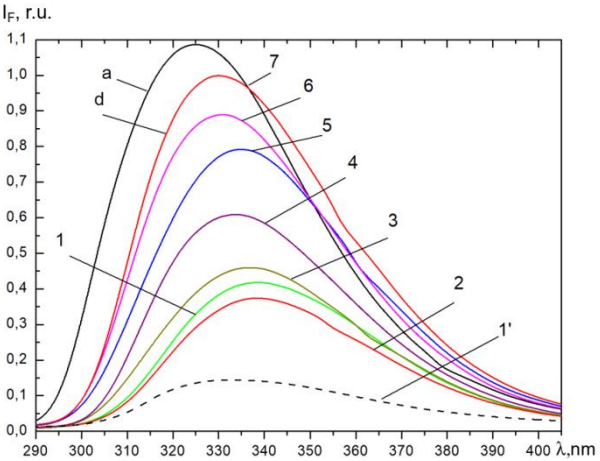

Fig. 3.5.

Fluorescence spectra of blood serum of the patient with a burn injury who was undergoing inpatient treatment in the St Luke Hospital in 2017 in the dynamics during the treatment (1 – 9.02, 2 – 14.02, 3 – 22.02, 4 – 27.02, 5 – 03.03, 6 – 10.03, 7 – 31.03), a patient with sepsis, who was treated in 2002 at Emergency Hospital (1' – 06.06), donor (d) and 20 % albumin solution (a).

Despite the intensive treatment, his condition deteriorated significantly during the first 5 days. This is evidenced by the decrease of the fluorescence intensity and a slight long-wavelength shift (Fig. 3.5, curves 1, 2). In comparison with the previous patient, in this case there was, most likely, a more noticeable EI. Thus, the treatment process was corrected for him, including infusions of a 10 % solution of donor albumin (February 15, 18, 26, and March 2, 100–150 ml each day). It is obvious that infusions of a sufficient amount of albumin allowed to improve significantly for this time the work of the body's detoxification systems, with subsequent normalization of endogenous albumin synthesis by the liver. As a result, the fluorescence intensity of the patient's BS increased gradually, and the long-wave shift leveled off (Fig. 3.5, curves 3–7). After that, the patient was discharged from the hospital in a satisfactory condition.

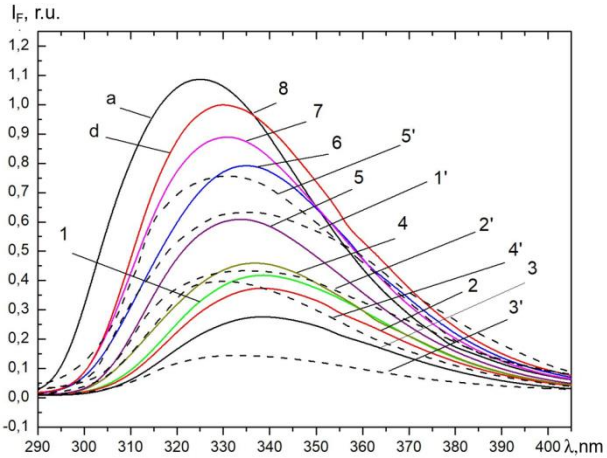

Fig. 3.6.

FS of BS of the patient with a burn injury who was hospitalized in the St Luke Hospital in 2017 in dynamics during the treatment (1 – 9.02, 2 – 14.02, 3 – 22.02, 4 – 25.02, 5 – 28.02, 6 – 03.03), donor (d) and 20 % donor albumin (a).

Fig. 3.5 (curve 2) shows that on February 14, a decrease of the fluorescence intensity and a slight long-wave shift of the FS were recorded within the framework of the MFS. If this fact was not taken into account and the infusion of donor albumin was not prescribed, bacteremia would increase and we would obtain curve 3 within the framework of MFS on February, 22 (see Fig. 3.5). This figure shows that the patient's condition has approached septic (curves 3 and 3' are quite close to each other). Due to the monitoring of the treatment process within the framework of the MFS, it was easy to identify a threatening situation for this patient. Therefore, it is necessary to prescribe several sessions of infusion therapy with a solution of donor albumin until the patient's health condition improves and until he recovers. The scenario of his treatment at the final stage took place under the supervision of the MFS and is illustrated in fig. 3.6. If the infusion of donor albumin had not been prescribed on February 22, his health could have continued to deteriorate. In this case, as in the previous one, the treatment should be continued using infusion therapy with a solution of donor albumin, although there is no guarantee of the successful completion of the treatment process in this case. In the case of absence of the possibility of monitoring the treatment process within the framework of the MFS, it is necessary to monitor properly the condition of patients and correct the treatment process in time by prescribing timely infusion therapy with a solution of donor albumin. At the same time, it is very important to carry out the detailed

monitoring of the patient's condition during the treatment and to correct the treatment process, if possible.

During the COVID-19 pandemic, there were difficulties in the treatment process of patients with burn injuries using MFS. Having analyzed thoroughly the results obtained during the treatment of patients with burn injuries within the framework of the MFS, in the St Luke Hospital, Center of Thermal Trauma and Plastic Surgery (V. S. Savchyn and N. V. Tuziuk) in 2018–2020 over 45 patients with burn injuries were treated using the treatment methods proposed by them. Special attention was paid to the use of infusions with donor albumin solutions. One of the comparison groups consisted of patients with burn injuries of I-IIAB degrees who were hospitalized in the stage of burn shock[94, 95, 96]. Thus, the clinical effectiveness of using xenoimplants saturated with silver nanocrystals, as well as the expediency of wide use of infusions with solutions of donor albumin, was proven[97].

CONCLUSIONS

Over the last thirty years under the auspices of the WHO, a lot of attention has been paid to the problem of the diagnostics and treatment of sepsis and burn injury. Significant improvement of the results of diagnostics of these diseases is still a fundamental problem of medical science. Unfortunately, most modern diagnostic methods are representative when manifestations of pathological processes are already visible. Basic research during the last decades has illustrated that spectral fluorescence is the most versatile method of biological spectroscopy. High sensitivity, accuracy, expressivity and simplicity of fluorescent characteristics cause special interest to the fluorescent analysis as an important method of modern and especially early diagnostics of purulent-septic complications.

A deep understanding of pathogenesis is a key point in the formation of a diagnostic strategy and treatment tactics for patients with various diseases.

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[94] Patent of Ukraine No. 102105 Method of treating wounds using lyophilized xenoderm transplants saturated with silver nanoparticles / V. S. Savchyn, O. V. Lukavetskyi, N. V. Huda, I. V. Stoyanovskyi, O. M. Chemeris, N. V. Tuzyuk, T. I. Farmaga. – 12.10.2015.

[95] Patent of Ukraine No. 10737 Method of lyophilization of xenoderm implants / V. V. Bihunyak, N. P. Luchanko – 1993.

[96] Tuziuk N. V. Evaluation of the effectiveness of lyophilized xenoderm implants saturated with silver nanocrystals in the local treatment of patients with superficial burn wounds / N. V. Tuzyuk // Scientific progress of medicine and pharmacy of the EU countries. – Czestochowa, Republic of Poland. – April 23–24, 2021. – P. 104–107.

[97] Chernii V. I. The role and place of albumin in modern infusion and transfusion therapy / V. I. Chernii // Medicine of non-urgent conditions. – 2017. – No. 1 (80). – C. 2–11. – p-ISSN 2224-0586, e-ISSN 2307-1230.

We paid considerable attention to the study of the pathological processes that occur in the bodies of patients with purulent-septic complications at the molecular level. It is based on the fact that in patients with these diseases, part of albumin molecules in their blood are blocked by toxins. The pathogenetic concept of the diagnostic and treatment model of purulent-septic complications was suggested. The main characteristics which we study with the MFS, are the fluorescence intensity (I_F) and the position of the maximum fluorescence band (λ_{max}) of the BS, which are functions of the concentration X of normal albumin molecules. A new approach to the diagnostics of sepsis is proposed, which consists of the definition of X* – extremely minimal value of the concentration of normal albumin, at which a septic state occurs. If $X \rightarrow X^*$, a protective reaction appears in the patient's body: the liver stops producing HSA and starts producing CRP. This biomarker stimulates immune reactions in the body, activates its defense systems and has a high correlation with the activity of the disease and the stage of the process. When interacting with bacterial ligands, macrophages are stimulated to produce TNF-α, IL-1β and IL-6. These pro-inflammatory biomarkers trigger a systemic inflammatory response, contributing to the transition to the SIRS state. At the same time, IL-6 also promotes the production of CRP. Proinflammatory mediators, including cytokines such as IL-6 and TNF-α, inhibit albumin production. It is important to note that there are still enough albumin molecules, capable to form complex in order to maintain the vital activity of patients and to detoxify toxins in the blood. When the patient's condition worsens, X decreases and the number of biomarkers increases significantly, and patients can move into the CARS state. We have already mentioned that in the papers, in which biomarkers were studied, no therapeutic measures were proposed that would ensure the recovery of patients. When X decreases and, accordingly, when the patient's condition worsens, the number of biomarkers increases significantly and patients can move into the CARS state.

The method of diagnostics of sepsis and purulent-inflammatory diseases was proposed within the framework of the MFS. Probable scenarios for the development of sepsis in patients with burn disease have been established. It is shown that the structure of the BS of fluorescence spectra in the patients with these diseases is an effective marker of its severity. This approach makes it possible to assess quickly the effectiveness of the treatment and, if necessary, to carry out its correction. The results obtained within the framework of the MFS for patients with sepsis are fundamental. It was found that in patients with severe sepsis, the fluorescence spectra have a two-peaked structure, which reflects the presence of two types of albumin molecules in the blood of patients. For the patients with purulent-septic complications, it was established that there is a correlation of spectral-

fluorescence characteristics of BS with integral clinical criteria of the severity of the condition and the phenomenon of verified bacteremia. At the same time, there is no correlation with standard biochemical parameters of conventional control of septic patients. The fluorescent characteristics detected within the framework of MFS have a pre-manifest nature, their changes were usually registered 24–48 hours before the appearance of obvious clinical and laboratory signs of a significant change of the general somatic status of patients.

When the patient's condition worsens, X decreases and the number of biomarkers increases significantly. In this regard, we offer complex diagnostics and treatment measures using infusions of donor albumin solutions. This will give us an opportunity to investigate more deeply the behavior of the spectral-fluorescence characteristics of BS and biomarkers in the septic area.

SUMMARY

A deep understanding of pathogenesis is the key point in the formation of the diagnostic strategy and treatment tactics for the patients with purulent-septic complications. We conducted a thorough analysis of the microscopic processes that occur in the blood of patients. The pathogenetic concept of the diagnostic and treatment model of purulent-septic diseases and a new interpretation of the experimental results for the spectral-fluorescence characteristics of the blood serum of the relevant patients were proposed. The results of the study within the framework of MFS of spectral-fluorescence characteristics of patients with sepsis and burn disease are presented and discussed. It is shown that MFS allows to diagnose properly purulent-septic diseases, including early ones. We have presented briefly the most important information about biomarkers and their use in the diagnosis of sepsis.

The modern approach for diagnosis and effective control of the treatment process within the framework of MFS and biomarkers using infusions of donor albumin solutions is proposed.

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