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SEPSIS ASSOCIATED ENCEPHALOPATHY AND ABDOMINAL SEPSIS: CURRENT STATE OF PROBLEM

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Abstract. The aim of the work is to analyze literature data on the current status of sepsis and sepsis associated encephalopathy (including against background of abdominal sepsis). For this purpose, 59 scientific publications of PubMed, Google Scholar and Research Gate scientific platforms were retrospectively analyzed.

Results of the study: Sepsis-Associated Encephalopathy (SAE) is a syndrome of general cerebral dysfunction, due to the systemic response of the body to the infection, with exception of direct CNS infection and other types of encephalopathies. In view of absence of unambiguous specific clinical criteria for SAE, its diagnosis is based on exclusion method that use a complex of instruments, including EEG, MRI, laboratory determination of NSE and S100b in blood. In surgical ICU, abdominal sepsis ranks second in levels of mortality. In accordance with the changes in sepsis nomenclature in 2016 and tactical approaches to the management of septic patients, the SOFA scale, which includes a systemic assessment of organ failure, including cerebral insufficiency, based on the GCS, is an optimal tool in assessing the condition of patients with suspected abdominal sepsis. At the same time, the GCS itself is considered to be the most optimal in assessing the severity of SAE. The degree of peritonitis severity is usually assessed separately, using the Mannheim Peritonitis Index. Data on the pathobiology of abdominal sepsis and SAE are based primarily on experimental studies and do not reflect a complete picture of the processes. Taking into account modern ideas about the "compartmentalization of the immune response" for sepsis, we should take a more balanced view of the interpretation of pathophysiological stereotypic reactions developing in different organs, and for clinical and experimental comparisons it is optimal to use similar conditions for the development of the septic process – for example, the abdominal source of sepsis.

Conclusion: Despite the significant contribution of abdominal sepsis and sepsis-associated pathology to the overall mortality rate of surgical ICU patients, as well as a large number of studies in this field, there is still no unambiguous opinion on the mechanisms of the development of a septic condition, and in particular, complications such as SAE . From the literature it is known that the triggering factor in the development of a septic cascade of events is the hyperactivation of inflammatory cytokines system, which has disadaptive nature and leads to the development of "cytokine storm". SAE is a consequence of this process. Damage to the CNS appears to be a complex process based on a complex system of neuro-immune-endocrine signals. In SAE morphogenesis a large number of white spots remain. In experimental studies, the role of damage of BBB, the reactivation of neuroglia as well as ischemic damage are emphasized. However, the deficiency of clinical-anatomical studies causes a certain discrepancy between the scientific concepts of sepsis, based on experimental models, and real clinical studies. "CLP" is recognized as the "gold standard" of the experimental animal model of sepsis and SAE, during which animals can recreate a close to the clinical picture of abdominal sepsis with cerebral dysfunction. Further clinical-anatomical and simultaneous experimental studies of abdominal sepsis and SAE will help to determine the thinner links of pathogenesis and morphogenesis of the sepsis-associated pathology of the CNS.

Keywords: sepsis associated encephalopathy, abdominal sepsis.

The topicality and the validity of the study. Sepsis is the main pathology treated in intensive care units (ICU), accounting up to 75% of all cases, and the leading cause of high mortality in these departments. According to J.A. Frontera, the mortality rate due to sepsis and its complications in the US reaches 750,000 cases per year [1]. The number of sepsis cases continues to grow and amounts approximately 10-14% of all incoming patients in the ICU in the countries of the Western world [2]. Despite the high rates of morbidity and mortality from sepsis, today there is still no clear understanding of the pathogenesis and pathobiology of this critical condition.

In the list of sepsis-associated syndromes, sepsis associated encephalopathy (SAE) is one of the most significant for predicting the course of the disease and planning of treatment interventions. During the development of sepsis, the central nervous system (CNS) is one of the first systems of the body that is involved in the pathological process [3]. SAE is the most common cause of delirium in ICU patients and is described in about 50% of patients with sepsis [4]. The clinical symptomatology of SAE has a potentially reversible character and in the acute period of development and can include a decrease in the level of consciousness, from delirium and sopor to coma, a decrease in cognitive abilities, impaired perception and memory, convulsive activity, and even focal neurologic symptoms. In some cases, the syndrome can have long-term effects in the form of a prolonged postseptic cognitive impairment [5-7]. Despite the significant relevance of SAE problem, the pathogenesis of acute cerebral dysfunction against the background of sepsis is still poorly understood and is the subject of scientific disputes [8].

Abdominal sepsis occupies a special place in the problem of septic states, which is characterized by high morbidity and mortality, being the second most frequent cause of sepsis-associated mortality in ICU departments [9]. In addition to the features of pathogenesis, this type of sepsis differs in that it is most often used as an interpretation of the "gold standard" of the animal model of sepsis and SAE.

Due to changes in the nomenclature, the classification of sepsis and new recommendations on the management of septic patients, proposed by the world scientific community in 2016 [10], there was an urgent need to revise some of the notions of mechanisms for the development of sepsis, the revision of definitions and tools for assessing the clinical course of sepsis associated pathologies.

The aim is to analyze the data of modern scientific literature on the concept of sepsis associated encephalopathy (including against the background of abdominal sepsis), as

well as experimental models proposed to reproduce this state in animals.

Materials and methods. Search of literature was conducted in the databases of PubMed, Google Scholar and Research Gate scientific platforms using the keywords: «sepsis associated encephalopathy», «sepsis classification», «abdominal sepsis», «delirium», «animal models» in various combinations. In retrospect, 59 scientific publications were analyzed. Scientific articles were analyzed and interpreted in accordance with the research objectives.

Results of the study and their discussion.

Sepsis-associated encephalopathy (SAE) is a syndrome characterized by general cerebral dysfunction due to the systemic response of the body to infection, with the exclusion of clinical and laboratory signs of direct infection of the CNS, its macroanatomical damage (cerebro-vascular pathology, craniocerebral trauma, etc.), as well as the presence of other types of encephalopathies (hepatic, alcoholic, renal, respiratory, diabetic, exotoxic, etc.) [11].

There are two most common names for cerebral disorders that accompany the septic process: sepsis-associated encephalopathy and sepsis-associated delirium. Despite the wide use of both terms in foreign literature, they should not be considered synonymous, since the neurocognitive pathological complex accompanying the septic state may include delirium only as one of its stages of development. Thus, in accordance with DSM-5, delirium is defined as an acute and unstable disturbance of attention and awareness that can not be explained by pre-existing neurological pathology and is not a manifestation of a severe disturbance of consciousness such as coma [12]. Encephalopathy, as a more general concept, in its understanding covers a wide range of neuropsychiatric pathology and is more suitable for use in this case. It should be noted that, in accordance with modern ideas of indirect CNS damage in the background of the septic state, the use of the term "septic encephalopathy" is incompetent, since this term should be understood as direct damage to the brain tissue by an infectious agent [11].

Diagnostic aspects of SAE. Due to the high probability of severe consequences of SAE, early detection of it helps to identify patients with a more unfavorable prognosis that require more rapid medical care and intensive care. The clinical symptomatology of SAE can vary widely and is nonspecific, which is explained by the fact that ICU patients are mainly under the influence of sedative therapy, and the decrease in cognitive abilities, delirium and coma may be manifestation of number other pathological conditions. The foregoing means that SAE is a diagnosis of exclusion and requires the detection of brain dysfunction, using clinical, electrophysiological and biochemical criteria. The most commonly used clinical scales are Glasgow Coma Scale, Confusion Assessment Method for the ICU, and GCS can also be applied to sedated patients [13]. Eidelman L.A. and co-authors in 1996 in their studies showed that the use of the GCS allows us to reliably predict the outcome of SAE, which caused the recognition of this scale to be the most optimal for use in the diagnostic algorithm for patients with SAE, as well as including it in the algorithm for assessing the course of sepsis in general [14,10].

The most sensitive method for diagnosing cerebral dysfunction under these conditions is an electroencephalography which changes have prognostic qualities with respect to the severity of SAE flow [15, 16]. The use of CT, MRI, MRS is also extremely effective in diagnosis, and in particular, in the differential diagnosis of SAE, since it allows one to diagnose foci of infarctions, tissue edema and foci of leukoencephalolysis and other more specific patterns [17,18].

Despite the common belief that biomarkers neuron-specific enolase (NSE) and S100 beta are promising in constructing an effective diagnostic algorithm, given the significant increase in their level in the blood and CSF in most cases of SAE [19], this fact is still ambiguous, because firstly, these molecules are themselves of little specificity, and secondly, their diagnostic value does not have unified confirmatory data and interpretations results in various studies [13].

Nomenclature of sepsis. The development of SAE, of course, presupposes the patient's sepsis.

In accordance with the Third International Consensus Definitions for Sepsis and Septic Shock-2016 (Sepsis-3), sepsis should be considered as a life-threatening organ dysfunction caused by a dysregulated host response to infection [10]. Thus, the concept of "severe sepsis" disappeared from the classification of sepsis, which previously designated a continuing sepsis-induced arterial hypotension that does not respond to adequate infusion support.

Septic shock, according to new formulation, should be defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality rates of more than 40%. Clinically, septic shock can be established when it is necessary to inject vasopressors to maintain a mean arterial pressure within 65 mm Hg. and more and plasma lactate level more than 2 mmol / l (> 18 mg / dL) in the absence of hypovolemia. It is known that about 50% of patients with sepsis diagnosis do not have signs of a syndrome of systemic inflammatory reaction (SIRS). In this connection, new definition of sepsis does not emphasize the severity of the symptoms of SIRS, which was previously part of the definition of sepsis. According to the 1991 nomenclature, sepsis was considered as a systemic inflammatory response to infection, not necessarily an inadequate response, not necessarily life-threatening, but which had the potential to transform into heavier forms such as severe sepsis and septic shock. Now the septic process, in fact, has only two degrees of severity of its manifestations: actually sepsis and septic shock, which significantly limits the diagnosis of sepsic status at earlier stages of its development, to the development of organ failure, and this can lead to a more severe course of the disease and its complications [20]. In addition, sepsis as such, if considered in accordance with new criteria, can sometimes take the form of a hidden state, since there are examples where signs of organ failure are not apparent, despite the presence of SIRS symptoms in patients with infection in disease clinical picture [21].

Some aspects of the immunological response in the pathogenesis of septic states. Sepsis can have multiple manifestations, and its pathophysiology is very complex. It is not a disease, but rather the syndrome, the implementation of which depends on conditions such as source of infection, age, sex, and concomitant comorbidities and other [10, 22, 23].

Over the past decades, a huge number of experimental studies devoted to elucidating the mechanisms of the immune response during sepsis [24-27].

The immune system of the body has general principles of reactivity regardless of the nature of the damaging factor, whether it is infectious agents or factors of non-infectious origin. In the conditions of infectious inflammation in the first stages of the process, there is a binding of microorganisms to superficial phagocytic Toll-like receptors (TLRs), which leads to the release of cytokines by the latter [23]. Thus Gram-negative bacteria lipopolysaccharide (LPS) and endotoxins have a tropism for TLR-4 receptor type, in turn, the cell walls of Gram-positive bacterial cell wall antigens (peptidoglycans and lipoteichoic acid) exhibit reactivity against TLR-2 type [28]. Toll-like receptors are a family of special pattern recognition receptors (PRRs) of cellular membranes of immunocompetent cells. TLRs play a key role in maintaining the functions of innate immunity and are responsible for recognizing not only infectious agents but also internal signaling molecules released by damaged cells. In addition to participating in the immune response, these cell

receptors are responsible for the realization of a number of other homeostatic functions, in particular, neurogenesis. It is known that under normal conditions in the brain TLRs are expressed by microglial cells, astrocytes, oligodendrocytes and neurons [29].

Such components of infectious pathogens as, for example, LPS or bacterial DNA are collectively referred to as pathogen associated molecular patterns (PAMPs) and are recognized by PRRs. Some endogenous molecules, such as the high-mobility group box (HMGB-) 1, hyaluronan and HSPs, can also be recognized by PRRs and can initiate activation of immune reactions [27]. These endogenous signaling molecules, which are termed alarmins, are analogous to exogenous PAMPs, but in their essence are normal components of cells that can be released into the extracellular space either during necrosis or during stress reactions. The last observation in 2002 formed the basis for the arguments for the development of the systemic inflammatory response of the organism in the absence of a significant effect of infectious pathogens [30]. Together, PAMPs and alarmins are put together in one group; called damage associated molecular patterns (DAMPs) [28].

Resident forms of macrophages and polymorphonuclear leukocytes initiate the primary immune response of the organism to infection, activating and involving in the process all new populations of phagocytic cells. Cytokines released by macrophage forms are the main regulators of the directivity and strength of the immune response. Among the proinflammatory cytokines IL-1, TNF-α, HMGB-1 and IL-8 should be stood out. Anti-inflammatory properties have IL-1 receptor antagonist (IL-1-ra) and IL-10. IL-6 has properties of both directions. Interacting with target cell membrane receptors, cytokines trigger a cascade of reactions leading to functional changes in the genetic apparatus of cells and their phenotypic qualities [31]. The most revealing of this is the overexpression of early response genes by the nuclear factor-κB (NF-κB). And, finally, NF-κB is able to directly activate the transcription of the family of interleukins, in particular, IL-1, 2, 6,12, as well as TNF-α.

Also, cytokines cause the expression of adhesion molecules on the surface of endothelial cells, promoting leukodiapedesis, which in turn is enhanced by the action of chemokines. In modulating the inflammatory process, matrix metalloproteinases (MMPs) play an important role [32]. MMPs potentiate pro-inflammatory reactions, on the one hand, carrying out proteolysis and activation of cytokines, and on the other - inducing the release of biologically active soluble adhesion molecules that modulate the binding of leukocytes to membrane adhesive molecules [33].

Previously, sepsis was considered a manifestation of hyperproduction of proinflammatory mediators, and the presence of these factors in the blood - the condition necessary to maintain the pro-inflammatory focus of the process as a whole. However, modern data indicate the duality of the pathogenesis of sepsis, in which anti-inflammatory mediators play an equally significant role in the complex immunopathological cascade, which has become known as the "cytokine storm" [34]. It is known that in the experimental models of sepsis, as well as in humans in septic state, the complement system is activated. Peter A. Ward, using such experimental models of sepsis as infusion of endotoxin and cecal ligation and puncture, has shown a dominant role of activation products one of this system factors, in particular C5 (C5a anaphylatoxin and the membrane attack complex, C5b-9) and the receptors to them - C5aR and C5L2 in the development of "cytokine storm" and multiorgan failure (MOF) in animals. In addition to MOF, other consequences of activation of this factor indicate the loss of congenital immunity functions by polymorphonuclear leukocytes, apoptotic death of lymphoid cells, disseminated intravascular coagulation and cardiomyopathy [35].

In accordance with modern concepts of septic state, the inflammatory response has its pathophysiological characteristics depending on the place where it unfolds - the concept of compartmentalization of inflammation [36]. In addition, studies in recent years indicate that analysis of the profile of plasma inflammatory mediators and signaling molecules can be used to formulate strategy for early detection of patients with bacteremia, identify the nature of the infection, and also to predict the clinical outcome of sepsis [21, 37].

The exact causes of organ failure development and death in patients with sepsis remain not completely clear, as pathogistological examination of the tissues of most organs indicates an insignificant percentage of cell death [27].

Pathophysiological basis of SAE. Precise mechanisms for the development of SAE are not unambiguous.

It is considered that CNS damage in this state is an indirect process, and encephalopathy itself is the result of metabolic changes and cellular signaling caused by components of the inflammatory response.

In general, in the pathogenesis of SAE, three principal categories of homeostatic disorders are distinguished: diffuse neuroinflammation, ischemic damage, and excitotoxicity [8, 38]. Among the total number of factors that are of cardinal importance in the mechanisms of encephalopathy development, such as an increase in the levels of cytokines and pro-inflammatory factors are indicated [39], damage to the BBB and impaired its permeability [40], endothelial dysfunction and vascular endothelial reactivation [41], oxidative stress [42], hemodynamic cerebral disorders [43], neurotransmitter imbalance [44], change in the levels of amino acids [45, 46], a violation of calcium homeostasis [45], mitochondrial insufficiency [47], penetration of bacterial endotoxins through the BBB [45], reactive changes in neuroglia, necrosis and apoptosis of neurons [8], cytotoxic and vasogenic edema of nervous tissue [45].

Of particular interest are studies aimed at identifying the reactions and features of individual regions of the brain involvement in the implementation of a systemic inflammatory response. It is known that in conditions of BBB safety, there are 2 main ways of inflating signals to the brain: vagal delivery to stem autonomous nuclei [48] and the activity of brain circumventricular structures (pineal body, subcommissural organ and subfornical organ, organum vasculosum, median eminence, neurohypohysis) devoid of barrier and being direct communicators between the immune system and brain tissue [49]. The third variant of the receipt of signaling information in CNS is the situation of the compromised BBB, when the activation and /or destruction of endotheliocytes is observed with the possibility of direct flow from systemic bloodstream into the brain tissue of immunocompetent cells, inflammatory mediators and neurotoxic substances. Under the conditions of infectious load, all three possible pathways are activated, and it seems that the vagus influence is crucial, affecting both autonomic and neuroendocrine systems, and through periventricular structures vagal effect spreads to the rest of the barrier-protected areas of the brain [48].

It is known that in cases of sepsis, there is a brainstem insufficiency, which may be a consequence of neuroinflammation due to an increased influx of inflammatory mediators into the brainstem tissue through area postrema. An excessive level of inflammatory mediators triggers the initiation of the processes described above, which morphologically can manifest in form of stem nuclei neuronal apoptosis, necrotizing leukoencephalopathy, and different degrees tissue edema [8, 38]. Also interesting are studies on the involvement of certain brain structures such as the hypothalamus, pituitary gland, amygdala, locus coeruleus, hippocampus, frontal cortex, white matter in the pathophysiology of SAE, where pathohistological, immunohistochemical and molecular-genetic traits are described in various, mostly experi-

mental, studies have shown the development in these areas of ischemic necrosis, apoptosis of neurons, their axonal damage, signs of microglial activation, reactive astrogliosis, neuroinflammation. It should be noted more frequent indications in studies on apoptotic changes in neurons in the autonomic centers of the brain such as the amygdala, nucleus solitarius and locus coeruleus [8, 38]. At the same time, the damage of these structures has a clear correlation with clinical symptomatology both in ICU and in postseptic patients.

It was experimentally shown that diffusely in the whole brain, in the microcirculatory vessels there are signs of separation of the neurovascular complex due to endothelial insufficiency, increased expression of aquaporin-4 in astrocytes, followed by their edema and an increase BBB permeability. Also, possible mechanisms for reducing the function of BBB in systemic inflammation, shown in experimental studies, include dysfunction of interendothelial tight junction protein complexes, such as occludin, ZO-1, ZO-2, claudin-3, claudin-5 [50].

It is assumed that a special role in the pathogenesis of SAE is played by astrocytic glia, which under normal conditions is responsible for a huge list of homeostatic functions ("homeostatic glia") in the brain. In conditions of brain tissue damage, it is also widely involved in the realization of many, often antagonistic, processes [51]. Also astroglia plays a major role in regulating the concentration of neurotransmitters in the brain tissue (primarily glutamate, GABA and glycine). In this regard, with astrogliosis development, as well as damage to vascular astrocytic processes and all astrocytic syncytium, as shown in experimental studies, neurotransmitter imbalance develops. On the other hand, high levels of cytokines, nitric oxide, and prostaglandins change the characteristics of neurotransmission, especially with respect to β-adrenergic, central muscarinic, glutamatergic, monoaminergic systems, GABAergic synapses, corticotropin releasing factor, vasopressin, adrenocorticotropic hormone and neurotrophic factors. Due to increased influx of aromatic amino acids into the brain tissue and their predominance over amino acids with branched side chain, there is an accumulation of false neurotransmitters and decrease in levels of norepinephrine, dopamine and serotonin with an unchanged level of GABA [13]. Also, concomitant metabolic disorders and drug toxicity in septic patients should be considered, which also leads to neurotransmitter imbalance.

Particular qualities of sepsis clinical diagnosis. For the clinical intrahospital determination of organ dysfunction in patients with suspected or confirmed infection, it is common to use the SOFA (Sequential [Sepsis-related] Organ Failure Assessment) scale (Table 1), an increase of 2 points or more indicates organ failure and increases the risk intrahospital mortality by more than 10% [10].

For patients admitted to ICU with suspected infection at the initial stages of complex diagnostics for rapid prognosis of the disease course, as well as planning of treatment activities, it is recommended to use the abridged SOFA (quick SOFA, qSOFA) scale, which does not require laboratory diagnostics. qSOFA includes the diagnosis of impaired consciousness, systolic blood pressure of 100 mm Hg or less, and respiratory rate of 22/min or greater.

Abdominal sepsis. In accordance with recommendations of the World Society of Emergency Surgery-2017 (WSES guidelines for management of intra-abdominal infections-2017), abdominal sepsis is a systemic inflammatory response of the body to intra-abdominal infection (IAIs) [52]. It should be noted that intra-abdominal infection is considered in two versions: uncomplicated and complicated intra-abdominal infection (cIAIs). Exactly latter variant, in which the infection goes beyond one organ, spreading to the peritoneum is the initial factor in the development of abdominal sepsis. In fact, a complicated intra-abdominal infection is represented by peritonitis (most often secondary), when an acute abdominal infection is caused by violation of the integrity of the gastrointestinal tract [52]. According to the WSES (World Society of Emergency Surgery) cIAIs Score Study (WISS Study-2015) data, an international multicenter observational study involving 4533 patients conducted in 54 countries and 132 medical institutions for 4 months (10.2014-02.2015), the main sources of intra-abdominal infection were the following (Table 2).

Table 1

SOFA Score

PaO2/FiO2 (mmHg)	**SOFA score**
<400	1
<300	2
<200 and mechanically ventilated	3
<100 and mechanically ventilated	4
Glasgow coma scale	**SOFA score**
13-14	1
10-12	2
6-9	3
<6	4
Mean arterial pressure (MAP) or administration of vasopressors required	**SOFA score**
MAP <70 mm/Hg	1
Dop ≤5 or Dop (any dose)	2
Dop >5 or Epi ≤0,1 or Nor ≤0,1	3
Dop >15 or Epi >0,1 or Nor >0,1	4
Bilirubin (mg/dl) [µmol/L]	**SOFA score**
1,2-1,9 [>20-32]	1
2,0-5,9 [33-101]	2
6,0-11,9 [102-204]	3
>12.0 [>204]	4
Platelets x 10^3/µl	**SOFA score**
<150	1
<100	2
<50	3
<20	4
Creatinine (mg/dl) [µmol/L] (or urine output)	**SOFA score**
1,2-1,9 [110-170]	1
2,0-3,4 [171-298, 305]	2

3,5-4,9 [300-440] (or <500 ml/d)	3
>5,0 [>440] (or <200 ml/d)	4

Table 2

Sources of IAIs In accordance with WISS Study [52]

Source of infection	Number (%)
Appendicitis	1553 (34.2)
Cholecystitis	837 (18.5)
Post-operative	387 (8.5)
Colonic non-diverticular perforation	269 (5.9)
Gastro-duodenal perforations	498 (11)
Diverticulitis	234 (5.2)
Small bowel perforation	243 (5.4)
Others	348 (7.7)
Pelvic inflammatory disease	50 (1.1)
Post traumatic perforation	114 (2,5)
Total	4533 (100)

Table 3

WSES sepsis severity score for patients with complicated Intra-abdominal infections (Range: 0–18) [53]

Clinical condition at the admission	
Severe sepsis (acute organ dysfunction) at the admission	3 score
Septic shock (acute circulatory failure characterized by persistent arterial hypotension. It always requires vaso-pressor agents) at the admission	5 score
Setting of acquisition	
Healthcare associated infection	2 score
Origin of the IAIs	
Colonic non-diverticular perforation peritonitis	2 score
Small bowel perforation peritonitis	3 score
Diverticular diffuse peritonitis	2 score
Post-operative diffuse peritonitis	2 score
Delay in source control	
Delayed initial intervention [Preoperative duration of peritonitis (localized or diffuse) > 24 h)]	3 score
Risk factors	
Age>70	2 score
Immunosuppression (chronic glucocorticoids, immunosuppresant agents, chemotherapy, lymphatic diseases, virus)	3 score

According to the WISS Study-2015, the WSES sepsis severity score was considered optimal for assessing the severity of sepsis in patients with cIAIs (Table 3).

However, given the new determinations of sepsis of 2016, this scale loses its uniqueness, since it contains items that do not correspond to the new nomenclature. In view of this fact, in order to assess the severity of the patient's condition and predict the clinical course of disease, there is again a need to use more universal, generally accepted scales that assess separately the severity of peritonitis (Peritonitis-Specific (Surgical) scores) and the severity of multiorgan failure associated with sepsis (General Organ Failure Severity scoring systems). Based on the data of most modern studies, the most optimal scale for assessing the severity of peritonitis is the Mannheim Peritonitis Index (MIP). Among the general scales for assessing the degree of organ failure in ICU patients, the SOFA scale is the most optimal for predicting the course of disease and development of a tactical management plan for patients with suspected abdominal sepsis [54].

It is known that, in spite of the fact that sepsis is a systemic reaction of the organism to infection; the features of the pathophysiological cascade of reactions can vary considerably depending on the localization of the primary septic focus. This issue has been very poorly studied and requires more in-depth study. The views on the main pathobiological mechanisms of abdominal sepsis are largely identical to those for sepsis in general; however, separate experimental and clinical studies indicate a primary temporal isolation of the immune response in the abdominal cavity at the initial stage of abdominal sepsis represented by secondary peritonitis. This is indicated by a combination of high levels of IL-1, TNFα, IL-6, IL-10 and IFNγ in the peritoneal fluid of patients with peritonitis and significantly lower concentrations of these cytokines in blood plasma [9].

SAE Experimental Models. To date, the most used models of sepsis and SAE are: 1) the introduction of infectious agents; 2) inducing endotoxemia; 3) cecal ligation and puncture (CLP).

The simplest method for simulating an inflammatory response in animals, similar to that in humans is induction of endotoxemia by intravenous or intraperitoneal administration of LPS. This method of studying the mechanisms of SAE differs in that, to a certain extent, it is permissible even in humans' studies [55]. However, as shown by the results of studies, temporal characteristics of cytokine profile changes in animals comparative to real conditions in patients with sepsis have significantly limits the interpretative possibilities of this model.

Intravenous or intraperitoneal administration of live infectious agents, usually bacterial ones (Escherichia coli - for Gram$^-$ sepsis and Staphylococcus, Pseudomonas - Gram+-sepsis), allows to investigate the influence of certain strains of microorganisms, their dose and site of primary infection for systemic immune response. However, this model requires the introduction of high doses of microorganisms and its implementation may depend on the individual sensitivity of the animal's organism to a specific infectious strain [56].

Currently, the CLP model is most often used [57], which suggests cecal ligation with subsequent perforation and the development of secondary polymicrobial peritonitis and abdominal sepsis [58]. This model is the "gold standard"

of sepsis and SAE reproduction, as it includes the effects of both necrotic and ischemic-altered intestinal tissue and fecal, polymicrobial peritoneal cavity colonization in animals to development of metabolic, vascular and systemic immunological reactions in many respects similar with those that develop in patients with abdominal sepsis [59].

Conclusions. Despite the significant contribution of abdominal sepsis and sepsis-associated pathology to the overall mortality rate of surgical ICU patients, as well as a large number of studies in this field, there is still no unambiguous opinion on the mechanisms of the development of septic state, and in particular, such complications as SAE. From the literature it is known that triggering factor in the development of septic cascade events is the hyperactivation of inflammatory cytokines system, which has disadaptive nature and leads to the development of a "cytokine storm". SAE is a consequence of this process. In this case, damage of CNS appears to be a complex process based on compound system of neuro-immune-endocrine signals. In SAE morphogenesis, a large number of white spots remain. In experimental studies, the role of BBB damage, the reactivation of neuroglia, as well as ischemic damage of brain tissue are emphasized. However, the deficit of clinical-anatomical studies causes a certain discrepancy between the scientific concepts of sepsis and its complications based on experimental models and real clinical studies, as well as trials of new therapeutic approaches that are not effective enough. "CLP" is recognized as the "gold standard" of the experimental animal model of sepsis and SAE, during which animals can recreate close to the clinical picture of abdominal sepsis. Further clinical-anatomical and simultaneous experimental studies of abdominal sepsis and SAE will help to determine the thinner links of pathogenesis and morphogenesis of the sepsis-associated pathology of the CNS.

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СЕПСИС АСОЦІЙОВАНА ЕНЦЕФАЛОПАТІЯ ТА АБДОМІНАЛЬНИЙ СЕПСИС: ПОТОЧНИЙ СТАН ПРОБЛЕМИ

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Резюме. Із метою аналізу даних літератури щодо сучасного стану питань сепсису і сепсис асоційованої енцефалопатії (в тому числі на тлі абдомінального сепсису) проаналізовано 59 наукових публікацій наукових платформ PubMed, Google Scholar та Research Gate.

Результати дослідження: Сепсис асоційована енцефалопатія (САЕ) – синдром загальної церебральної дисфункції, обумовлений системною відповіддю організму на інфекцію при виключенні прямого інфекційного ураження ЦНС і інших енцефалопатій. Діагностика САЕ неспецифічна і заснована на методі виключення з використанням комплексу інструментів, включаючи ЕЕГ, МРТ, лабораторне визначення NSE і S100b. У хірургічних ВІТ абдомінальний сепсис займає друге місце за рівнем смертності. Відповідно до рекомендацій з ведення сепсису 2016р. оптимальним інструментом оцінки стану хворих з абдомінальним сепсисом є шкала SOFA, що включає в себе посистемну оцінку органної недостатності, в тому числі і недостатності ЦНС, засновану на ШКГ. При цьому ШКГ саму по собі прийнято вважати найбільш оптимальною в оцінці тяжкості САЕ. Ступінь тяжкості перитоніту прийнято оцінювати окремо, використовуючи Мангеймський індекс перитоніту.

Висновки: Патогенез сепсису і його ускладнень залишається предметом суперечок. Пусковим фактором у розвитку септичного каскаду подій і САЕ є «цитокіновий шторм». Пошкодження ЦНС видається комплексним процесом, заснованим на складнопідрядній системі нейро-імунно-ендокринних сигналів, але в морфогенезі САЕ залишається велика кількість білих плям. В експериментальних дослідженнях показана роль пошкодження ГЕБ, реактівізації нейроглії і ішемічного ушкодження. «Цекальне лігування з пункцією» визнано «золотим стандартом» експериментальної тваринної моделі сепсису і САЕ, в ході якої у тварин відтворюється близька до клінічної картина абдомінального сепсису з церебральною дисфункцією.

Ключові слова: сепсис асоційована енцефалопатія, абдомінальний сепсис.

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СЕПСИС АССОЦИИРОВАННАЯ ЭНЦЕФАЛОПАТИЯ И АБДОМИНАЛЬНЫЙ СЕПСИС: ТЕКУЩЕЕ СОСТОЯНИЕ ПРОБЛЕМЫ

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Резюме. С целью анализа данных литературы о современном состоянии вопросов сепсиса и сепсис ассоциированной энцефалопатии (в том числе на фоне абдоминального сепсиса) проанализировано 59 научных публикаций научных платформ PubMed, Google Scholar та Research Gate.

Результаты исследования. Сепсис ассоциированная энцефалопатия (САЭ) – синдром общей церебральной дисфункции, обусловленный системным ответом организма на инфекцию при исключении прямого инфекционного поражения ЦНС и других энцефалопатий. Диагностика САЭ неспецифична и основана на методе исключения с применением комплекса инструментов, включая ЭЭГ, МРТ, лабораторное определение NSE и S100b. В хирургических ОИТ абдоминальный сепсис занимает второе место по уровню смертности. В соответствии с рекомендациями по ведению сепсиса 2016г. оптимальным инструментом оценки состояния больных с абдоминальным сепсисом является шкала SOFA, включающая в себя посистемную оценку органной недостаточности, в том числе и недостаточности ЦНС, основанную на ШКГ. При этом ШКГ саму по себе принято считать наиболее оптимальной в оценке тяжести САЭ. Степень тяжести перитонита принято оценивать отдельно, используя Мангеймский индекс перитонита.

Выводы. Патогенез сепсиса и его осложнений остается предметом споров. Пусковым фактором в развитии септического каскада событий и САЭ является «цитокиновый шторм». Повреждение ЦНС представляется комплексным процессом, основанным на сложноподчиненной системе нейро-иммунно-эндокринных сигналов, но в морфогенезе САЭ остается большое количество белых пятен. В экспериментальных исследованиях показана роль повреждения ГЭБ, реактивизации нейроглии и ишемического повреждения. «Цекальное лигирование и пункция» признано «золотым стандартом» экспериментальной животной модели сепсиса и САЭ, в ходе которой у животных воссоздается близкая к клинической картина абдоминального сепсиса с церебральной дисфункцией.

Ключевые слова: сепсис ассоциированная энцефалопатия, абдоминальный сепсис.

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