

Sepsis: Principles of Diagnosis

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The success of the treatment of a patient depends on the proper identification of the pathological process and its complications on time.

The procedure of the diagnostics is carried out according to a nosological principle, which is the basic principle of medicine. The other basic principles are also to be taken into account during the procedure of the verification of a certain pathological processes. First, it is necessary to determine the origin of the pathological process and the class it belongs to in accordance with the international classification of diseases (cardiovascular diseases, respiratory diseases, cancerous diseases, infectious disease etc.). The most important requirement for diagnosis is identification of the etiology of the disease. For example, in case of an infectious disease this determines the accuracy of the diagnosis and subsequent adequate antibiotic therapy. One of the main basic principles is pathogenetic. The pathogenesis (mechanisms of development) of the disease is a kind of pathologic process. The pathologic process of inflammation is a basis of infectious diseases and infectious complications. A necessary requirement for accurate diagnostics includes the clinical-morphological principle. That means, there are specific clinical symptoms and morphological changes in tissues and organs typical for a certain disease. Therefore there is a certain algorithm, which should be used in the diagnostics of diseases.

The critical conditions are often followed by infectious complications. According to the present criteria many of them are regarded as sepsis. The results of the analysis of mortality in England for the period of 2001-2010 showed that 5.1% of deaths in the country were associated with sepsis [1], which is one of the most serious health problems according to the authors. In the United States sepsis is on the 11th position [2] in the list of the most frequent causes of death. A retrospective analysis was used to identify the incidence of sepsis among 150410 patients for 6-year period (2005–2010). In the countries of Western Europe the number of patients with sepsis annually exceeds 500 000. Mortality in sepsis reaches 28.6% and increases up to 38.4% with age. [3,4]. At the same time, the clinical diagnosis of sepsis in deceased patients is not always confirmed by the results of postmortem studies. We analyzed the medical cards and protocols of autopsies of 134 patients who had died in intensive care units. Infectious complications were registered in 129 patients, in 16 of whom sepsis was diagnosed. At postmortem examination only one case of sepsis was confirmed [5]. This shows us the significant overdiag-

nosis of sepsis, that is just as dangerous as those cases, when the pathological process is not identified.

Recently there have been some encouraging reports of more cautious and careful evaluation of developing infectious complications that can be regarded as sepsis. At the international forum in Beijing (2011), it was noticed [6] that the point in the understanding and definition of the term «sepsis» is different among doctors of different specialties. The process of determination of sepsis was based on the concept of systemic inflammatory response (SIR) adopted in 1991, which seemed to be simple before it turned out to be come much more complicated. According to the concept, the diagnosis of sepsis is registered when fever, leukocytosis, and tachycardia and tachypnea in combination with an infectious process are present. The main problems of the proposed concept are the low specificity and excessive sensitivity. According to the specified criteria the majority of cases of critical conditions are to be regarded as sepsis. This definition of sepsis is confusing and creates terminological and diagnostic difficulties. According to the authors, the term of «sepsis» should be reviewed to meet the clinical realities and pathogenetic processes, developing in cases of sepsis.

The determination of sepsis on the basis of this concept has three main problems [7]. First, the high sensitivity of the SIR causes almost 90% of patients in intensive care units meet the criteria of sepsis. Second, the fact that there is an inflammatory process in all patients with sepsis, which is widely recognized, but, obviously, not all patients with infectious process have sepsis, is also contradictory. Third, non-infectious diseases (traumas, burns, pancreatitis, autoimmune diseases, organ transplantation and others) are also accompanied by certain clinical signs of SIR as well as infection. On the basis of proposed clinical signs it is impossible to distinguish changes developing in case of non-infectious from the ones developing in case of infections because they are based on the same immune reactions, disorders of coagulation, injuries and regeneration of certain tissues.

In 2013, the Committee of agreement, composed of 68 international experts representing 30 international organizations, offered the updated program of treatment of sepsis and septic shock [8]. Attention was paid to the importance of conformation of bacterial infection and potential sources of infection. Sepsis was defined as the presence of confirmed or probable infection along with its systemic manifestations. The signs reflecting the «systemic infection» were not specified. Attention was paid to methods of treatment of severe sepsis and septic shock.

There is a need in a more detailed randomization of patients with sepsis diagnosis when including them in investigations [9]. The majority (61) of clinical reviews (102) were excluded from consideration because, when conducting addi-

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tional randomized controlled trials, they did not meet the quality criteria. Moreover there was no criteria for inclusion and data on the severity of the disease. The authors concluded that the definition of sepsis should be based on more specific criteria of individual characteristics of patients to treat patients more successfully and to reduce the mortality rate.

According to the diagnostic algorithm the reason of sepsis is a certain infection. According to the international classification of disease the diagnosis of sepsis should include the information about its etiology (staphylococcal, streptococcal, pseudomonas etc). The clinical peculiarity of sepsis is its acyclicity. This means a significant changes of temperature and leukocytosis (increases follow decreases). That is not typical of the manifestation of an infectious process and reflects signs of generalization of the infectious process. Sepsis is characterized by certain morphological changes. Based on the analysis of a large amount of clinical data Academician N. K. Permyakov concluded that the morphological sign of generalization of purulent infection is the formation of metastatic purulent foci localized in blood vessels including those that cause the development of parietal endocarditis and polypous-ulcerative valvulitis. The only kind of sepsis is its metastatic form that indicates the generalization of the infectious process. At postmortem examinations purulent thrombophlebitis and multiple isolated septic foci with the involvement of small veins situated in the proximal direction are seen. That can be regarded as metastasis of purulent process [10].

In all cases of postmortem examinations the primary metastatic focus that can be localized in the area of the penetration of the infection or metastatic purulent foci should be identified. The hyperplasia of lymphoid tissue also occurs. Attention should be paid to the enlargement of the spleen (in 2–3 times), which gives a significant scraping. In case of sepsis, purulent metastatic foci found in different organs and tissues are also registered. If the morphological signs of sepsis are absent, the presence of other reason not linked with sepsis and playing a leading role in tanatogenesis from tanatos - death must be proved.

The main morphologic criteria for sepsis include formation of a septic focus, metastatic foci of purulent inflammation in various organs and tissues, and a significant spleen enlargement [11]. Thus an important task of the diagnostic of sepsis is the development of methods of intravital visualization of morphological changes that characterize the infectious process. Intravital visualization of structural changes developing in different diseases is widely used for diagnostics of various diseases and is performed by various methods: computer tomography, magnetic resonance, ultrasonic methods of diagnostics, endoscopy, the examination of microcirculation, various kinds of biopsies, angiography, the use of isotopes and etc).

In case of sepsis it is easy to identify the source of inflammation and to determine the size of the spleen. The problem of *in vivo* detection of septic and metastatic foci of purulent inflammation is more complicated.

Recently have been published some encouraging messages showing the possibility of *in vivo* detection of inflammation in internal organs using perfluorocarbon emulsions. Russian perfluorocarbonic emulsion «Perforan» has been successfully used in clinical practice [12–14].

Experimental data demonstrating the possibilities of *in vivo* detection of the inflammation in the lungs have been obtained [15]. Pneumonia in mice was caused by intratracheal exposition of lipopolysaccharide (LPS). Perfluorocarbonic emulsion containing fluorine-19 was injected intravenously to detect inflammatory foci in the lungs by the method of magnetic resonance. The accumulation of perfluorocarbonic emulsion by macrophages in the foci of inflammation was confirmed by histological methods. It was shown that macrophages in the area of inflammation engulf particles of perfluorocarbonic emulsion, which works as a contrast agent when using magnetic resonance method [16, 17]. The authors concluded that the use of perfluorocarbon emulsions containing fluorine-19 was a highly specific prognostic test that allowed to quantify the distribution of inflammation in the lungs *in vivo*.

The results of the study of phagocytes detection *in vivo* using perfluorocarbonic emulsion by the method of magnetic resonance in experimental ischemic damage of myocardium and brain have been published [18]. The model of acute ischemia of a myocardium and brain in mice with subsequent intravenous injection of perfluorocarbonic emulsion has been employed in the study. Histological studies show that particles of the emulsion are engulfed by macrophages and accumulated in the area of the myocardial and brain ischemia. Perfluorocarbon emulsions containing fluorine-19, have certain advantages. The fact is that perfluorocarbonic emulsions are non-toxic and can be used for diagnostics of various inflammations and the observation of biological processes at the cellular level.

Bi-colour fluorescent perfluorocarbonic nano-emulsions that increases the efficiency of their detection and employs the method of magnetic resonance were proposed [19].

There have been numerous recent studies of molecular markers in critical conditions, including various infectious complications, for example sepsis [20–24]. However, the specific molecular markers for sepsis have not been found so far. Apparently, the dynamics of different molecular markers (cytokines, procalcitonin and others) concentration in inflammatory diseases, including sepsis, reflects the processes of regulation and of adaptation and, first of all, the condition of immunoreactivity of the human body.

Thus, based on the mentioned above, we propose the following definition of sepsis. Sepsis is an polyetiologic process characterized by acyclicity, formation of focus of infections and generalization of infection that occur infections as a result of developing foci of purulent inflammation in various internal organs.

Subsequent research in this field will facilitate performing the diagnostic programs and optimizing the treatment of infections complication of critical illness.

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Submitted 13.09.13