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The Main Reason for the Problem of Infusions in Sepsis

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In recent decades, sepsis has become one of the global health problems with a negative growth trend. Currently, according to the World Health Organization (WHO), sepsis is diagnosed annually in 49 million people worldwide, whose treatment in 11 million cases does not save from death (1). In the United States, over the past 6 years, the number of cases of sepsis has remained at the same level, amounting to 1.7 million cases annually, however the number of deaths during this period increased from 270 thousand (2) to 350 thousand (3). An even higher mortality rate is observed among patients with septic shock, whose rates in Europe and North America, that is, in the most advanced healthcare systems, reach 38% (4).

Sepsis belongs to the category of extreme situations, and one of the first aid methods for such patients is intravenous infusions, the purpose of which is to increase the volume of circulating blood and restore impaired microcirculation in tissues (5-8). The need for intravenous infusion of solutions to patients with septic complications has a completely logical justification and in the most severe cases is carried out in the form of boluses, however, the results of such therapy do not always achieve the desired effect and often bring results directly opposite to expected (9-12). In this regard, over the years, numerous and constantly repeated attempts have been made to find out which volume of solutions, limited or free, is preferable and brings optimal benefits. The results of such studies are based on analytical comparisons of a huge number of patients, but no patterns and differences in infusion therapy of the two main groups of observations can be identified (13-18).

In many works devoted to determining the optimal volume of intravenous infusions in patients with septic complications, the authors express a tendency to limit the amount and speed of fluid administration. However, such preferences are by no means a consequence of research results, but only reflect the unpredictability of the results of such therapy, which indicates empirical caution in determining the infusion load. At the same time, the principle of conducting such studies is initially programmed for heterogeneity of results and the impossibility of obtaining specific and unambiguous conclusions. To understand the reason for the existing misconceptions in this matter, it is necessary to return to the origins of the whole problem.

So, sepsis is currently interpreted as a result of the body's reaction to infection, which is accompanied by the development of potentially life-threatening conditions (19). At the same time, sepsis is now considered as a homogeneous pathology, and patients with this diagnosis receive standard therapy of the same type. However, no matter how sepsis is presented as a separate disease or a peculiar syndrome, and no matter how the causes of its development are emphasized on the immunology of the body, the characteristics of its pathogens and other factors, one characteristic of this process remains very important for a differentiated assessment of such patients. As you know, sepsis does not belong to the primary independent diseases, but acts as a complication of various other inflammatory processes, does it not? In this regard, it should be borne in mind that in each case of sepsis, its occurrence will be preceded by different prerequisites and mechanisms for the development of the general pathological process.

If we look at the seemingly homogeneous contingent of sepsis patients from this angle, then, first of all, it is impossible not to distinguish two fundamentally different groups in the total mass according to their prerequisites and mechanisms of development of the primary underlying disease. As is known, on the one hand, the process of inflammation and subsequent tissue transformation is based on a local vascular reaction with a change in blood flow in them and an increase in wall permeability. On the other hand, inflammatory processes can occur in the basin of both circulatory circles, which are diametrically opposed to each other in their anatomical and functional features and their role in the body. However, despite the obvious anatomical and functional antagonism, the two circulatory circles can provide vital needs of the body only in close interaction, constantly maintaining the necessary inverse proportions between each other. In the last connection, it should be recalled that the most sensitive areas responding to the slightest changes in volumetric blood flow and blood pressure are concentrated in the immediate vicinity of the heart, which allows reflexively, automatically and autonomously maintaining vital parity of cardiac output between the two halves of the heart.

One of these sensitive areas, which reacts to the slightest changes in blood pressure in a small circle, are the baroreceptors of the pulmonary vessels. These sensitive elements located in the wall of the pulmonary vessels cause the so-called unloading reflex, which was first described almost a century ago and is one of the earliest adaptive reactions to the first signs of changes in blood flow in the small circle (20). The main effect of this reaction is blood retention in the periphery due to a decrease in systemic vascular tone and a decrease in venous return. Such a restructuring is accompanied by unloading a small circle and maintaining the proportions between the two halves of the cardiovascular system, which happens unnoticeably to our attention, timely saving our body from the suddenness of a critical situation. Like any autonomous adaptive system, this restructuring of the general blood circulation in the body develops in parallel with the rate of increase of the pathological process and in the most aggressive cases is able to exceed its permissible limits, creating additional problems. Since the described mechanism of changes in blood circulation is reflected in peripheral microcirculation and indicators of systemic pressure, such a picture corresponds to modern criteria of sepsis and septic shock. However, unlike septic causes, this variant of shock has a completely different mechanism, which has long been presented in the literature as pulmonogenic (21,22).

There are no areas in the large circle of blood circulation in which the tendency to change blood flow indicators would instantly threaten the body with the development of a situation incompatible with life support. In this regard, the systemic circulation is not provided with an adaptive mechanism identical to the small circle, since there is no such urgent need for it. The causes of the primary violation of systemic blood flow may primarily stimulate humoral adaptation factors. The combined effect of an excess of such factors, coupled with impaired general circulation, ultimately leads to damage to the pulmonary circulation and the development of acute respiratory distress syndrome. The nuances of the scenarios presented can serve as a basis for further research and discussion, but their overall strategic direction and differences have received objective evidence and have successfully passed clinical trials (21,22).

An additional confirmation of the presented differences in the mechanisms of general circulatory disorders, depending on the localization of the primary focus of inflammation, can be statistical materials on the initial nosologies of sepsis in a few publications dealing with this topic. Basically, the authors analyzing the problem of sepsis claim that the main disease, as a result of which most septic complications develop, is community-acquired pneumonia - CAP (23-29). Only some

studies provide statistical data on pneumonia as the main cause of sepsis, which accounts for 50% to 68% (30-33). Noting the undoubted predominance of CAP among the causes of sepsis, some studies have attempted to identify the pathogen in the blood. Such studies bring very interesting results: among cases with diagnosed sepsis, it is in patients with CAP, unlike other diseases, that blood cultures turn out to be sterile (34,35), and positive reactions are observed in only a few percent (36-38). In such patients, even in the case of septic shock, bacteremia is detected only in 13.2% - 18% (39,40).

In connection with the latter, it should be noted that the results of bacteriological blood tests are currently not crucial for the diagnosis of septic complications, but are more intended for the use of targeted antibacterial therapy, reflecting the prevailing priority of ideas about the decisive role of the pathogen in the development of inflammatory processes and their complications. The basis for determining septic complications is made up of various scoring schemes based on the assessment of a number of functional indicators (41-44). In such diagnostic systems, indicators of respiratory rate and systemic blood pressure are of leading importance. At the same time, if shortness of breath is not a characteristic sign for inflammatory processes in the periphery and its appearance should be regarded as the appearance of new mechanisms of the pathological process and the development of complications, then for AP this symptom is considered typical and is consistently observed not only in severe patients. On the other hand, a decrease in blood pressure in the most severe patients with AP can be registered already at the earliest stages of the disease, being secondary shifts in relation to the primary focus and reflecting compensatory changes (see above). In the case of peripheral inflammatory processes, the tendency to arterial hypotension is no longer compensatory, but pathological in nature, requiring adequate correction.

The presented comments on the diagnosis of complications, despite the absolutely obvious differences between AP and other inflammatory processes, as well as completely different pathogenesis of the clinical picture of these diseases, are currently not taken into account. This is due to the prevailing stereotype about the main role of their pathogens in the development of such diseases and the crucial importance of etiotropic therapy. Not so much a paradox as the tragedy of such a situation lies in the fact that, regardless of the existing directly contradictory differences in the pathogenesis of processes, medical care is carried out on the basis of uniform general therapeutic principles. Infusion therapy, which, according to current recommendations, begins at the early stages of the development of severe forms of AP, gives the opposite effect to what is expected, since it increases venous return, stimulating the mechanisms of the disease (21,22). In modern publications on the results of CAP treatment, one can find the revelations of the authors and statistical data reflecting the ineffectiveness of existing approaches to providing medical care to this contingent.

Usually, when presenting the results of treatment of septic patients, the authors of such articles are not inclined to pay special attention to their own failures, so such comments are relatively rare. For example, some reports draw attention to the fact that pneumonia continues to progress after hospitalization, despite treatment (45,46). P.-Yu. Boëlle et al. (47) noted that 2 days after hospitalization in general therapy departments, 25% of patients with AP were transferred to emergency departments from- for the deterioration of the condition. In other studies, the authors conclude that if, despite therapy for 72 hours, the condition of patients continues to deteriorate, then we can talk about the disadvantages of etiotropic treatment and sepsis (35,48). Among such publications, there are even reports that many patients with AP developed septic shock already

during treatment, which did not exist at the time of hospitalization (27,49). Finally, it should be noted that the general recommendations for infusion therapy in sepsis provide for the use of vasopressors in case of failure. This scenario is most typical for patients with AP, since additional blood flow to the small circle area will stimulate the unloading reflex.

To the above materials, it remains only to add the ancient postulate that if treatment does not bring the expected effect, then this type of treatment does not correspond to the nature of the disease. In the presented materials, we are talking about a significant deterioration in the condition of patients with AP in a relatively short period of time. The author of these lines has observed similar cases in his own practice, and they were quite reasonably attributed to the negative results of treatment and, above all, to the negative effect of infusion therapy. Examples of such observations and additional evidence are presented in a number of articles by the author published in recent years, which can be found in the public domain. A more detailed description of such situations is given in the monograph (22).

Based on the above brief description of the pathogenesis of AP, it is possible to understand the cause of the negative effects of infusion therapy in this category of patients. However, at present, contrary to the existing prerequisites for revising the concept of this disease and the principles of its treatment, these misconceptions are being further developed. The unprecedented growth of viral forms of AP in recent years has led to the automatic transfer of diagnostic schemes for sepsis and its treatment complex without any objective evidence and convincing scientific justification of its viral nature (50-53).

The discrepancy between the pathogenesis of AP and the principles of its treatment is a very obvious reason that a number of specialists consider this disease to be a situation with the highest risk of death among all other nosologies and note that the prognostic capabilities of clinicians are limited at the same time (54-56). Such conclusions logically follow from widespread practice, when methods that can stimulate its further development are traditionally used in the treatment of acute inflammatory process. These circumstances are also, in my opinion, one of the main reasons why, for example, sepsis remains the main diagnosis of hospital mortality in the United States (57). At the same time, the enormous work of a large group of American specialists to clarify the causes of the negative effects of infusion therapy in sepsis has not brought concrete and clear results (17).

To solve this long-overdue problem, it is absolutely necessary to reconsider the concept and principles of treatment of patients with AP. However, the apparent simplicity of solving such an important problem in connection with the inevitability of a radical change in established and entrenched views must certainly encounter skeptical rejection of new beginnings. Therefore, in order to ensure the need for a separate solution to the problem of sepsis in patients with AP, unlike all other inflammatory processes, it is necessary to re-audit infusion therapy for sepsis not in the total mass, but after dividing all observations into two specified groups. For the purity of the comparison, patients with previous chronic and severe pathology of the heart and lungs can be excluded. There is no doubt that such a re-analysis of the results will reveal noticeable differences between the two groups. The further process of conceptual correction will reduce the number of septic complications primarily due to their verified diagnosis, since currently the number of patients with sepsis is artificially increasing due to its overdiagnosis in patients with AP.

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