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Short Communication

What are the Next Steps in the Diagnosis of Sepsis?

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In recent years, several papers and reviews on biomarkers for sepsis have been published [1,2]. The conclusion is unambiguous - currently, we do not have a sufficiently sensitive and specific parameter for infectious inflammation. However, transcriptome studies have shown that gene expression in infectious and non-infectious inflammation is different [3,4]. So, what is the problem? It is the current availability of parameters used for the measurement in plasma or serum, which should be specific for infectious inflammation. This availability is given, among other things, by the technologies we use to determine these biomarkers.

What is the current situation in the diagnosis of sepsis? We use two approaches to diagnose sepsis. The first performs the detection of biomarkers associated with the body's inflammatory response, while the second performs direct diagnosis of infectious agents. In both cases, we encounter several problems. In the first case, we do not yet have a parameter that is specific to the infectious aetiology. Sepsis is defined as an inappropriate immune response to an infection. So, what should biomarkers for sepsis show? They should define or interpret this inappropriate immune response. What is the reality, more precisely, what are our current options? We are able to detect and measure the inflammatory activity of an organism, where the most mentioned and measured biomarkers for sepsis in a clinical practice are procalcitonin and C-reactive protein [5]. Using these parameters, we determine and measure the intensity of the inflammatory response, which is, however, not specific to the infectious aetiology. Many non-infectious diseases are associated with an elevation of these biomarkers. Autoimmune diseases, cardiovascular diseases, but also iatrogenic effects such as surgeries or therapies are associated with an increase in these parameters [6,7]. The determination of procalcitonin and C-reactive protein is now the gold standard, but sensitivity and specificity are not sufficient in any of them. We still only reach between 75 and 85%, which means that every fifth or sixth sample is a false positive or a false negative.

Microbiological examination methods have significantly reduced the time required for diagnosis in the case of a direct detection of infectious agents, but this is still not sufficient. Methods in molecular biology can detect the presence of infectious agents within a short time, but there are other limits - such as the inability to determine antibiotic susceptibility.

Availability and sensitivity of methods

In sepsis, diagnosis speed plays a crucial role in the resulting outcome. Sepsis biomarker testing must be available 24 hours a day without delay. If we look at the technologies that we currently use for detection, we can highlight turbidimetry, nephelometry or immunoassays. No new parameter has been discovered in the last 20 years, the determination of which would bring significant progress in the diagnosis of sepsis. However, the use of molecular methods, specifically proteomics, provides new possibilities for the detection of parameters that are not detectable by these methods [8]. Nevertheless, it is possible to determine and measure these parameters by mass spectrometry, with relatively low operating costs. An example is the determination of arachidonic acid [9]. The non-use of immunological parameters in the diagnosis of sepsis is a paradox. Although sepsis is defined as an inappropriate response of the immune system to an infection, the determination of immunological parameters in clinical practice is minimal. Repeated studies have shown that these parameters are important and useful in both the diagnosis of sepsis and the patient's prognosis. The determination of immunoglobulins

is a simple and affordable test providing a result within tens of minutes after sampling. Hypogammaglobulinaemia is a predictive factor of adverse patient outcome, with the possibility of targeted intravenous immunoglobulin replacement therapy [10]. Expression of CD64 on neutrophils is an excellent parameter for diagnosing sepsis [11]. Determination of HLA-DR expression on monocytes is a parameter of the so-called "immunoparalysis", and its significance for the patient's prognosis has been repeatedly proven [12]. The limit is flow cytometry technology, which is not available under 24 hours.

Improving the diagnosis of sepsis will bring us i) the use of proteomics to detect new parameters, the quantity of which we are not able to measure by current methods - nephelometry, tubidimetry ii) the use of mass spectrometry to quantify them.

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