LETTER TO EDITOR

Sepsis In Critically Ill Patients – From Molecular To Clinical View

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Introduction

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. It used to be known as systemic inflammatory response syndrome (SIRS) or bacteremia, but the second definition is not suitable, because now the presence of microorganisms in blood is not necessary to diagnose sepsis [1-3].

The most common causes of sepsis are infections located in the abdomen, lungs, urinary tract and central nervous system. Over 50% of cases is caused by Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*, but also Gram-positive bacteria (mainly *Staphylococci*), viruses and *Mycobacterium tuberculosis* can contribute to this dangerous state [1-5].

Signs and symptoms include: fever, increased heart rate, tachypnoea and confusion.

There may occur other symptoms related to the organ in which infection is taking place.

When it comes to critically ill patients, the signs and symptoms may not be so specific. These patients are particularly vulnerable to metabolic acidosis, low blood pressure (which may lead to septic shock), higher cardiac output and dysfunction of the blood coagulation.

Sepsis is the most common cause of death in group of patients who have been hospitalized, especially in the intensive care units. Severe sepsis may be the reason of more than 200 000 deaths per year (USA) [2,4].

Sepsis as molecular damage

The infection causes a complex reaction of the organism which depends on the pathogen (quantity and infectivity) and the specific features of the patient (genetic characteristics, chronic diseases, function of the immune system). The host response to sepsis is characterized by both proinflammatory responses and

antiinflammatory immunosuppressive responses. The proinflammatory response can result in dysfunction of the organs and the antiinflammatory response (significant for local restriction and systemic damage of tissues) may cause decreased resistance to secondary infection [1-4].

Pathogens activate the immune cells and can interact with pattern-recognition receptors. These receptors recognize structures located in microorganisms known as pathogen associated molecular patterns, which initiate the innate immunity. The same receptors identify particles released from injured cells (damage associated molecular patterns) called alarmins such as S100 proteins, extracellular RNA and DNA [1-3].

Severe sepsis may lead to disorders of the coagulation system resulting in disseminated intravascular coagulation. Growth factor is responsible for this process by using the malfunction of the protein C, antithrombin and fibrinolytic system. The association between DIC and infection are regulated by protease activated receptors (the main is PAR-1).

The antiinflammatory reaction causes the immunosuppression in patients, who survived the severe sepsis. This can result in inability to heal the primary infection despite the proper antibiotic therapy and activation of hidden infections, which might worsen the patient's condition [1-6].

Sepsis in clinical outcome

Sepsis is the most common cause of MODS, over 90% of MODS is due to sepsis. However, it is not so clear why patients with sepsis or SIRS may develop MODS. It is believed that some genetic predispositions can potentiate the receptors' expression which disrupt intercellular pathways. Activated neutrophils by their adhesion molecules join the endothelium, which begins release of graininess and endothelial damage. Endothelium becomes permeable and there is an inflow of leukocytes, macrophages and lymphocytes from blood vessels to interstitial space which results in organs' damage. At the same time, prothrombotic factors activate the complement and coagulation system, which causes microvascular thrombosis. The result of the low blood pressure and low cardiac output is organ hypoperfusion and hypoxia which increase organs' failure. The most common, dominant symptom of MODS is primary lung damage and due to that state, respiratory failure [1-3].

75% of Acute Respiratory Distress Syndrome is caused by sepsis. It is a severe reac-

tion of lungs to factors initiating their damage which often turns into pulmonary oedema. It is caused by proinflammatory reactions, in which cytokines like TNF alpha, interleukins etc. act chemotactically and activate neutrophils which migrate to lungs and secrete oxidants, proteases and leukotriens. What is more, during ARDS, epithelium is getting permeable, which provides fluid inflow into the alveoli. Damage of pneumocytes type II disturbs ion transport and the fluid can not be evacuated from lungs. Pulmonary oedema plays the lead role in mortality in patients with ARDS [4-6].

Sepsis biomarkers

The biomarkers used to diagnose sepsis must have high sensitivity and specificity and suit in appropriate criteria. One of the most important factors are test availability, simplicity and possibility of a quick result. The most common biomarkers in sepsis are: C-reactive protein, procalcitonin, interleukins, miRNA and CD64 receptors [2-6].

CRP is an acute phase protein, which the highest level is observed 1-3 days after the beginning of the infection. This protein in sepsis can reach the level even thousand times higher than the upper limit of the norm. This mark is also useful to differentiate bacterial and viral infection and has a prognostic value [1-4].

Procalcitonin (PCT) is a peptide, which increases its level in blood 2-4 hours after infectious insult to the tissues. Short time of detection allows to early start of antibiotics or surgical intervention. PCT is also significant in differentiation of sepsis caused by Gram-negative (very high level) comparing to Gram-positive bacteria (lower increase).

Interleukins such as IL-27 and IL-6 have also a meaningful role in sepsis diagnosis. IL-27 is used to detect sepsis in critically ill patients. However, this interleukin increases more in critically ill children. In combination with PCT improved the ability of both biomarkers to identify the patients with sepsis, which source is not located in the lungs. IL-6 level may be elevated several dozen times during inflammation. It is a very useful marker in sepsis due to its pyrogenic and proinflammatory properties [1-6].

CD64 receptors, which are expressed on neutrophils and monocytes, are specific for bacterial infections and have a diagnostic utility for sepsis. Higher level is correlated with worsening severity of sepsis [4-6].

There were many researches to discover the meaning of miRNA in sepsis diagnosis.

Several miRNAs and their target proteins are indentified as an indication of severity of sepsis.

In addition, independently from biomarkers, it is necessary to collect blood cultures to detect the right pathogen and start targeted treatment [1-6].

Future directions

Early detection of sepsis is one of the most important factors, because when the diagnosis is confirmed, the targeted therapy can be implemented, which may result in faster recovery and reduced mortality. To detect sepsis, doctors use the SOFA scale, which is a simple, fast and non-invasive method which consists of 6 parameters: partial pressure of oxygen, number of platelets, quantity of bilirubin, Glasgow scale, MAP and level of creatinine/diuresis. When there is a high possibility of death, there should be used the qSOFA scale, containing 3 parameters: disturbances of consciousness, systolic blood pressure ≤ 100 mmHg and tachypnoe ≥ 22 per minute. When the 2 of 3 symptoms are presented, the sepsis can be confirmed. Procalcitonin test should be done, because it may detect the sepsis but it also has a predictive value [1-6].

When it comes to the prevention, there were many researches to find the perfect solution to decrease the possibility of occurrence of sepsis. A high-dose of vitamin C is seemed to play a lead role, because of the ability to augment antibacterial defense and mitigate oxidative injury-induced microcirculatory impairment [1-6].

Conclusions

Sepsis is a very severe condition, which may lead to many serious life-threatening com-

plications, including organs' failure and acute respiratory distress syndrome or end in death. It is very important to diagnose it as soon as possible to prevent side effects and reduce the mortality. Now it is more likely to detect it at an early stage, thanks to many biomarkers which have high sensitivity and the result comes within few hours. Early implementation of appropriate pharmaceuticals and high-level quality of care can improve the patient's condition and reduce the risk of death due to sepsis.

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