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Advances in the diagnosis of sepsis

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EDITORIAL

Inevitably, sepsis has still remained one of the major challenges at the Intensive Care Units (ICUs) (1). About 30 million cases per year are estimated worldwide and this tendency is continuously increasing (2). Although sepsis is known for a long time, its pathomechanism is not completely understood due to the various triggering factors and also to the altered response of the individuals with different underlying diseases.

In sepsis with bacteremia, endotoxins (LPS) of Gram negative microbes and exotoxins from Gram positive microbes play a major role in the development of the symptoms. Currently, it is thought that pathogenesis of sepsis includes microbial interaction with the host defense system before bacteria can enter the bloodstream (3-5). Defense mechanisms in tissues differ from those of the intravascular ones. In the tissues (e.g. first in localized infections) leukocytes are the main antimicrobial factors while in the bloodstream fight against bacteria is mediated by humoral factors on the surface of erythrocytes. Bacteria that can invade the circulatory system possess

antioxidant enzymes (SOD, catalase, etc.) protecting them from oxidative injury exerted by the host. In the bloodstream invading bacteria are attached to the surface of erythrocytes stimulating oxygen release (from oxyhemoglobin) that might kill bacteria by oxidation. If bacteria escape oxidation they enter erythrocytes by permeabilizing the membrane. Once inside the erythrocytes bacteria are most probably to be killed due to the high concentration of oxygen. On the other hand, bacteria might survive inside the RBCs at poor oxygenation or when bacteria are resistant to oxidation. In this way, RBCs may form a bacterial reservoir where they can further proliferate (6,7). Inside the erythrocytes bacteria are protected from most of the antibiotics and the antibacterial factors of the host. Bacterial proliferation damages erythrocytes with a subsequent release of the microbes into the bloodstream (or to other erythrocytes). In case of bacteremia a premature release of oxygen from erythrocytes and an oxidation resistant infection might occur. As a consequence, sepsis and in severe cases, septic shock will develop. Further oxidation of plasma proteins and lack of proper oxygen content in erythrocytes may cause injury of distant organs leading to multi-organ failure (MOF) (8,9).

These events are also strongly related to the development of a misbalance between the inflammatory and anti-inflammatory cascade especially when tissue injury (major surgery, trauma, burns, pancreatitis, etc.) is present. From the laboratory part, only a few parameters are used routinely for early detection of sepsis from the more than 200 sepsis related biomarkers, namely pro-inflammatory and acute-phase proteins (CRP, procalcitonin, interleukines) (10-14), pentraxins (15,16), cytokine/chemokine biomarkers (IL-6, IL-8, IL-10, TNF- α, etc.) (17,18), macrophage migration inhibitory factor (19,20), high-mobility-group box 1 (HMGB1) (21,22), coagulation biomarkers (23,24), triggering receptor expressed on myeloid cells 1 (TREM-1) (25,26) and midregional pro-adrenomedullin (27). Up to now, no single marker or a combination of the above markers proved to be specific and sensitive enough for timely diagnosis of sepsis. Furthermore, the ultimate need to predict the outcome of the disease or to monitor therapeutic efficiency by laboratory testing has not been fulfilled completely.

The uncertainty regarding both clinical and laboratory diagnostic criteria has led to the establishment of new sepsis guidelines in 2016. Among the diverse findings and explanations in sepsis, the only true fact is, that diagnosis with proper decision making should be performed within the shortest possible time. The sooner the antibiotic therapy is begun the higher chance for the patient to survive. In order to fulfil this requirement both clinical and laboratory findings (including microbiological identification) are equally important.

In this issue of the *eJIFCC*, there are four manuscripts which summarize the present knowledge on the major aspects of diagnosis and treatment of sepsis with the introduction of some unconventional new biomarkers. The first manuscript of Trásy and Molnár highlights sepsis management from the point of view of intensive therapy. The paper is focusing on the important aspects of the new sepsis guidelines and on the pathophysiology of the disease. The authors describe the body's immune response to pathogen invasion (pathogen-associated molecular patterns: PAMP and damage-associated molecular patterns: DAMP). The role of procalcitonin (PCT) in the diagnosis and antibiotic treatment is discussed in details. Professor Molnár and his group have been involved in the research of diagnostic and prognostic markers of sepsis for more than 15 years with special emphasis on the clinical usage of PCT (28,29).

In the next paper Rogić and her co-authors, besides the classical CRP and PCT markers highlight the potential use of presepsin as a recent laboratory parameter for early detection of sepsis. Presepsin is a 13 kDa soluble form of CD14 cluster surface glycoprotein derived mainly from membrane bound CD14 on the surface of monocytes (mCD14). Presepsin enables the binding of LPS and the LPS-binding protein (LBP) complex to toll-like receptors (TLRs), augmenting the inflammatory response. Even if the clinical usefulness of presepsin has not been verified in every detail yet, the major advantage of this test lies in the very early rise of presepsin in sepsis (within 1 hour). Another advantage of the test is that measurement of presepsin can be done at the bedside with a POC method. Professor Rogić's basic fields of research and professional activities are evidence-based laboratory medicine, organization and management of medical biochemistry laboratory, point-of-care testing, and organization and management of laboratory parameters of renal diseases. The next review of Kustán et al. deals with unconventional biomarkers with potential clinical usefulness at the ICU. A challenging observation in sepsis and septic shock is the release of large amounts of a physiological intracellular protein, actin into the circulation. Once freed from the cells, excess actin is toxic and enhances the risk for respiratory distress syndrome, forming of micro emboli and development of multiple organ dysfunction syndrome (MODS). Excessive actin release into the bloodstream decreases the level of the actin scavenger proteins gelsolin and Gc globulin. In septic patients, especially with acute kidney injury (AKI) urinary actin level is strongly associated with kidney status. In critically ill patients, urinary alpha-1-acid glycoprotein or orosomucoid (u-ORM) as an inflammatory marker is extremely elevated and may be considered as a non-invasive marker for diagnosis of sepsis. Kustán and his co-authors have worked out an automated immune turbidimetric assay for measuring of u-ORM and that of gelsolin is under development (30). Finally, the manuscript of Miha Košir and Matej Podbregar are discussing the function and clinical usage of a less known gaseous transmitter, hydrogen sulfide. Besides NO and CO, hydrogen sulfide (H_2S) is the third known gasotransmitter molecule influencing many physiological processes such as maintenance of vascular tone, modulating the inflammatory response, scavenging reactive oxygen species, etc. Its plasma concentration has a predictive value for the outcome of sepsis. Interestingly, too high or too low plasma H_2S levels exert unfavorable effects predicting the severity of the disease and indicating a worse outcome. Professor Podbregar and his team are attempting to place successful basic research into clinical context including interest in pathophysiology of shock, hemodynamic stabilization, prediction of severity of shock, cytokine removal techniques/modulation of inflammation and bioactive gases (NO, H_2S). They are also interested in development of point of care prediction tools.

In conclusion, the successful diagnosis and treatment of sepsis is based on the correct interpretation of clinical signs and symptoms and also on the availability of laboratory tests with high specificity and sensitivity. Measurement of one lab parameter is never enough and monitoring of key markers such as procalcitonin is essential. The tendency (rising or falling) of the biomarker is usually more important than the absolute values. Further evaluation of presepsin in comparison with well-established markers (PCT, CRP) and with possible interfering factors (kidney failure) is of utmost importance. The introduction of non-commercially available tests as u-ORM, gelsolin, Gc globulin and H_2S into the routine laboratory palette inevitably would give valuable complementary data for sepsis management.

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