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EDITORIAL II

Biomarkers of sepsis, a never-ending story

In this issue of the Romanian Journal of Anaesthesia and Intensive Care, Tomescu et al. reported a patient who developed septic shock after cephalic pancreatectomy in whom the use of cytokine-adsorbing column (CytoSorb) in combination with CVVH managed to re-establish the disturbed balance between pro- and anti-inflammatory cytokines [1]. In the same issue, Trancă et al. reviewed the value of biomarkers in diagnosing sepsis in trauma patients [2].

The topic of biomarkers is an old and at the same time a new debate in the literature. The identification of an "ideal" biomarker able to predict or facilitate early diagnosis of sepsis in trauma patients is still a challenge for researchers. Sepsis is the most frequent cause of late death in polytrauma patients [3].

In trauma, both pro-and anti-inflammatory mediators play a role. The systemic inflammatory response syndrome (SIRS) in trauma is characterised by a pro-inflammatory state. At the same time an anti-inflammatory response may follow associated with immune suppression. If the inflammatory response becomes exaggerated it is followed by a multiple organ dysfunction syndrome (MODS) [3, 4].

Several biomarkers have been evaluated for prediction, diagnosis and prognostic of sepsis [4, 5]. Among them, the cytokines and the acute phase reactive proteins, procalcitonin (PCT) and C-reactive protein (CRP) are the most studied biomarkers of inflammatory response and sepsis.

Unlike septic shock where the cascade of cytokine is well defined, the role of cytokine in trauma is not well elucidated [5]. In trauma patients there is conflicting evidence in the usefulness of IL-6 in predicting septic complication: however, high levels of IL-6 are correlated with a bad prognosis and an increased risk of mortality [4, 6, 7]. From the inflammatory chemokine, IL-8 appears to be a helpful marker for distinction between SIRS and sepsis in polytrauma [8]. Elevated values of interleukin-10 (IL-10) as an anti-inflammatory cytokine seem to be correlated with a high risk of sepsis and MODS [3, 9].

A more efficient biomarker for early recognition of sepsis in trauma patients is procalcitonin (PCT) [2, 10]. The absolute PCT value is influenced by many factors such as severity of injury [6, 11, 12] or gender [13]. The trend of PCT rather than a single determined value appear to be the best indicator for septic complications after trauma. The persistent high level or secondary increases after the peak values reached in the first 24-48 h after trauma are adequate predictors of sepsis and multiple organ failure [6, 14].

In contrast to PCT, the CRP levels are not able to early predict septic complications in trauma patients [6, 11]. The values are non-specifically elevated after trauma and can be used only for monitoring the general evolution of the clinical outcome [4].

Several other potential biomarkers of sepsis have been studied but evidence is limited. Some of these (aminoterminal proC-type natriuretic peptide – NT-proCNP, pancreatic stone protein/regenerating protein-

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PSP/reg) seem to be very promising in predicting early sepsis in trauma patients [11, 15].

The excellent review by Trancă et al. [2] highlights the importance of early diagnosis of sepsis and septic complications in polytrauma patients and the necessity for new biomarkers with an increased diagnostic value.

Another topic on debate is the efficacy of the haemoadsorption procedures to improve the balance of pro and anti-inflammatory cytokines in SIRS and sepsis. Until recently, no specific therapy for cytokine removal has proved its efficacy. The use of membranes designated for renal replacement therapy (CVVH) did not reduce the cytokine level [16]. The newly designed haemoadsorption columns, such as CytoSorb are the new tools used to modulate the immunological response in SIRS and sepsis.

The cytokine-adsorbing columns demonstrated excellent adsorption rates for inflammatory cytokine as TNFα, IL-1β, IL-6 and IL-8 in experimental and clinical studies when "cytokine storm" was present [17-22]. Moreover, in spite of the fact that clinical data are still scarce, the cytokine-adsorbing columns seem to be effective in restoring haemodynamic, and preventing or treating organ failure in critically ill patients [23-25]. One of the most studied cytokine-adsorbing columns in sepsis and septic shock is CytoSorb.

In their interesting case report, Tomescu et al. [1] showed that the use of cytokine adsorbing column (CytoSorb) in combination with continuous veno-venous haemofiltration in a patient with postoperative septic shock and multiple organ dysfunction after cephalic pancreatectomy, was followed by the decrease of pro-inflammatory cytokine levels especially IL-1β, IL-6, TNFα while the level of anti-inflammatory IL-10 was maintained within the normal-high level. According to the recent published data, the cytokine-adsorbing columns (CytoSorb) have less influence on the IL-10 level [22].

The authors reported that the level of interferon gamma, MCP-1, GM-CSF and the biomarker of sepsis (PCT and CRP) were also reduced correlating with a decreased level of WBC.

Another important issue demonstrated by the authors was the improvement of the haemodynamic parameters (cardiac output and systemic vascular resistance) and reduction of vasopressor support after each session of CVVH with CytoSorb filter.

The presented data suggest that a combination of CytoSorb with CVVH could restore the balance between pro- and anti-inflammatory cytokines, which is most likely responsible for the improvement of the haemodynamics.

This case report addressed an important issue regarding the role of cytokine adsorbing columns in the treatment of cytokine storm, modulation of the immune system and potentially prevention or treating organ failure. Further investigations and clinical trials are required in order to establish the overall benefits of haemoadsorption procedures in SIRS and sepsis and to assess their impact on long-term outcome and survival.

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