Sepsis diagnosis and monitoring – procalcitonin as standard, but what next?

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Abstract

Sepsis is a life-threatening organ dysfunction caused by a systemic altered host response to infection. According to the newest guidelines the sepsis treatment should be personalized and based on an approach specified by use of biomarkers to tailor therapy to each patient's needs. The main features of such biomarkers should be high specificity, sensitivity and ability to monitor the progress of sepsis. There is limited application of procalcitonin (PCT), C-reactive protein (CRP) and interleukin-6 (IL-6) for reaching this target, because of their secretion during non-infectious processes. The purpose of this review was to introduce four biomarkers, i.e. kallistatin, testican-1, presepsin and mid-regional pro-adrenomedullin, and compare their usefulness in diagnosing sepsis with PCT, CRP and IL-6.

Key words: sepsis, biomarkers, monitoring, mortality.

Anestezjologia Intensywna Terapia
2019; 51, 4: 305–311

Otrzymano: 24.06.2019,
zaakceptowano: 02.09.2019

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Sepsis is defined as a life-threatening organ dysfunction caused by an altered host response to infection and is a worldwide major health problem with high morbidity and mortality. It is highlighted that sepsis is a syndrome shaped by pathogen and host factors, characteristically changing over time, with diverse etiology, severity and prognosis [1]. Early diagnosis and appropriate management are the most important factors influencing sepsis survival rate in the intensive care unit (ICU). The newest definitions of sepsis/septic shock do not indicate any gold standard biomarker for sepsis diagnosis and monitoring but the heterogeneity of the septic patient population suggests that multiple biomarkers should be used to evaluate the dynamics of sepsis, therapy effectiveness and finally improve the outcomes [2]. Many biomarkers implicated in clinical practice are not sufficiently specific to differentiate sepsis from other non-infectious and inflammatory disorders. The commonly used biomarkers, such as procalcitonin (PCT), C-reactive protein (CRP) and interleukin (IL)-6, with different timing of release, present limited sensitivity and specificity [3].

Procalcitonin is a prohormone of calcitonin and in healthy individuals PCT is produced in thyroid C cells, from a calcitonin gene-related peptide I (CALC-1) located on chromosome 11. The mRNA product is known as preprocalcitonin. It is further modified to 116-amino acid procalcitonin, and all the PCT formed in thyroid C cells is converted to calcitonin, so no PCT is released into the circulation and its level in healthy subjects is very low (0.05 ng mL^{-1}). During systemic infection PCT is produced mainly by two alternative mechanisms: the direct pathway induced by lipopolysaccharide (LPS) or other toxic metabolites from microbes and the indirect pathway induced by various inflammatory mediators such as IL-6, tumor necrosis factor-α (TNF-α), etc. [4]. The increase of PCT was observed in 3–4 hours after intravenous injection of endotoxin and was maintained for 24 hours in healthy volunteers [5]. The measurement of PCT helps to guide and shorten the antibiotic therapy in septic patients [4], but recent studies showed that use of PCT did not affect the frequency of diagnostic or therapeutic procedures [6]. Additionally, the cut-off range of PCT concentration for sepsis confirmation depends on clinical settings, source of infection and co-morbidities [4].

C-reactive protein level may be increased during both infectious or non-infectious processes and in contrast to PCT, the hepatic synthesis of CRP starts 6 to 8 hours after onset and peak concentrations are reached between 36 to 50 hours after infection has started. The half-life of CRP is 19 hours and it is cleared by the liver [7].

Interleukin-6 belongs to the group of pro-inflammatory cytokines. Similarly to TNF-α and IL-1 it is an endogenous pyrogen but in contrast to them it has a longer half-life [8]. The synthesis of IL-6 is regulated by various factors, including endotoxin,

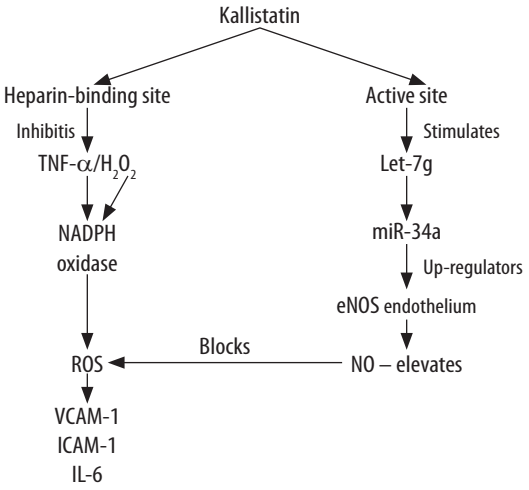
Należy cytować anglojęzyczną wersję: Mierzchała-Pasierb M, Lipińska-Gediga M. Sepsis diagnosis and monitoring – procalcitonin as standard, but what next? Anaesthesiol Intensive Ther 2019; 51, 4: 299–305. doi: https://doi.org/10.5114/ait.2019.88104

which stimulates its formation in monocytes and fibroblasts as well as glucocorticoids which inhibit its formation [9]. The highest level is achieved most often in 2-3 hours after stimulation with endotoxin [10]. IL-6 is considered as useful in septic patients but increase of its level is not specifically linked to infectious conditions [11].

The aim of our review was to provide the current information about kallistatin, testican-1, mid-regional pro-adrenomedullin and presepsin biomarkers that potentially replace or might be added to commonly used sepsis biomarkers.

CHARACTERISTICS OF KALLISTATIN

Kallistatin is a newly discovered member of the serpin (serine proteinase inhibitor) superfamily, and is an acidic glycoprotein with molecular mass of 58 kDa that exhibits high homology in amino acid sequence with other serpins, such as α_1-antichymotrypsin, α_1-antitrypsin, protein C inhibitor, and thyroxin-binding globulin [12]. Kallistatin is mainly synthesized in the liver and is secreted rapidly into the circulation, and to a lesser degree it is produced in blood cells, renal proximal tubular cells, colonic and prostatic tumor cells. It occurs in many human tissues, including the eye, kidney, liver, heart, arteries and veins, atheroma, blood cells and body fluids. The normal plasma level of kallistatin in healthy subjects, measured by a specific ELISA, is 22.1 ± 3.5 μg mL^{-1} [13]. According to the results of Chao *et al*. [13], a significantly reduced kallistatin level (7.2 ± 2.5 μg mL^{-1}, $P < 0.001$) was seen in plasma samples from 9 patients with liver disease and 10 patients with sepsis (7.7 ± 3.5 μg mL^{-1}, $P < 0.001$).



TNF-α – tumor necrosis factor α, ROS – reactive oxygen species, NADPH oxidase – nicotinamide adenine dinucleotide phosphate oxidase, eNOS – endothelial nitric oxide synthase, NO – nitric oxide

FIGURE 1. Kallistatin reveals antioxidant and anti-inflammatory activity. TNF-α potentiates ROS generation by activating NADPH oxidase on the surface of endothelial cells. Kallistatin stimulates eNOS synthesis through inhibition of miR-34a in endothelial cells. eNOS through NO formation reduces intracellular superoxide levels, inhibiting NADPH oxidase activity

Kallistatin displays double-edged activity in angiogenesis, apoptosis and oxidative stress, depending on cell types and pathological conditions. Kallistatin is identified as anti-inflammatory agent and a major tissue kallikrein inhibitor regulating its bioavailability and catabolism in the circulation [14, 15].

It has two structural elements: an active site and a heparin-binding domain, and kallistatin via its heparin-binding site interacts with cell surface heparan sulfate [13].

Kallistatin competes with TNF-α binding to cultured endothelial cells through its heparin-binding domain, blocking TNF-α-induced NF-κB activation, expression of the pro-inflammatory gene and the inflammatory response [16]. The heparin-binding site of kallistatin blocks high mobility group box 1 (HMGB1)-induced inflammatory gene expression in endothelial cells [17]. Kallistatin increases endoprotective miRNA Let-7g synthesis and through Let-7g induction stimulates eNOS, causing inhibition of oxidative stress and inflammation in endothelial cells (Figure 1) [18]. Possibly kallistatin through active site interaction with tyrosine kinase stimulates Let-7g synthesis. Kallistatin's active site was found to be crucial for stimulating a negative regulator of inflammation suppressor of cytokine signaling 3 (SOCS3) expression in macrophages through activation of a protein kinase C-extracellular signal-regulated kinase (ERK) signaling pathway, illustrating the mechanism by which kallistatin protects against sepsis-induced organ damage [19].

Role of kallistatin in sepsis

Chao *et al.* [13] observed reduced kallistatin levels in liver disease (9 patients: 7.2 ± 2.5 μg mL^{-1}) and in sepsis (10 patients: 7.7 ± 3.5 μg mL^{-1}). According to authors the decreased levels of kallistatin during sepsis might suggest its involvement in the protective mechanisms preventing the blood pressure decrease [13]. Additionally, the studies of Lin *et al*. [20] with 54 patients revealed that kallistatin is consumed in patients with severe CAP (community-acquired pneumonia) requiring ICU admission and its levels are linked to CAP severity. Additionally, in non-survivors kallistatin concentrations were significantly lower compared with survivors. The obtained correlations demonstrated that reduced levels of kallistatin from the first study day were accompanied with decreased levels of antithrombin III and protein C, and increased levels of IL-1, IL-1β and CRP. Lin *et al*. [20] revealed that decreased levels of kallistatin were associated with increased severity and worse outcome of septic pa-

tients. In another study by Lin *et al*. [21], results for plasma kallistatin levels on day 1 of ICU admission were lower in patients with septic shock compared with patients with severe sepsis ($P = 0.004$). Twenty-nine patients who died in the hospital had significantly lower day 1 kallistatin levels than patients who survived ($P = 0.031$). Using the optimal cut-off value (4 μg mL^{-1}) of day 1 plasma kallistatin determined by receiver operating characteristic (ROC) curves for 60-day mortality, it was found that high kallistatin levels were associated with a preferable 60-day survival ($P = 0.012$) by Kaplan-Meier analysis and lower Sequential Organ Failure Assessment (SOFA) scores over the first 5 days in the ICU ($P = 0.001$). High kallistatin levels were also independently associated with a decreased risk of septic shock, the development of acute respiratory distress syndrome, and positive blood cultures [21].

Li *et al*. [17, 22] revealed that kallistatin pretreatment attenuated kidney injury, inflammatory gene expression and mortality in association with increased SOCS3 expression in the lung and kidney of mice with polymicrobial infection or LPS-induced endotoxic shock in CLP-induced septic mice. The authors concluded that their results revealed a protective role and unique mechanisms of kallistatin in mortality, systemic inflammation and multiorgan damage in mice with established sepsis [17, 22]. According to the animal model results of Li *et al*. [17, 22], therapy with kallistatin may lead to the reversal of sepsis induced injury and is a possible novel strategy for sepsis treatment in humans, but its anti-inflammatory action needs to be more explored as a potential therapeutic approach for sepsis.

CHARACTERISTICS OF TESTICAN-1

Testican-1 is a highly conserved chimeric proteoglycan bearing chondroitin and heparan sulfate chains. It was first identified in human seminal plasma, and initially named as the precursor of seminal plasma glycosaminoglycan-bearing peptide and SPOCK [23]. The name SPOCK derives from the modular character of its core protein, which is composed of four SPARC/osteonectin domains and CWCV (Cys-Trp-Cys-Val amino acids sequence) and Kazal-like domains [23]. Testican-1 is a member of the BM-40/SPARC/osteonectin family of extracellular calcium-binding proteins. High expression of testican-1 is observed in the thalamus of the brain, and it is up-regulated in activated astroglial cells of the cerebrum [24]. Human and mouse testican-1 exhibit 94% amino acid sequence homology [25]. *In vitro*, it was observed that the *N*-terminal region of testican-1 may inhibit membrane-type 1 matrix metalloproteinase activation of matrix metalloproteinase-2 [26].

Testican-1 role in sepsis

Viewing the database of publications, there has been found only one article related to the significance of testican-1 in sepsis. As the first, Lee *et al*. [27] reported the statistically significant differences between healthy subjects (6.97–8.77 ng mL^{-1}) and septic patients, and between sepsis (20.44–63.37 ng mL^{-1}, $n = 30$) and severe sepsis (41.30–98.69 ng mL^{-1}, $n = 22$) or septic shock (98.10–151.85 ng mL^{-1}, $n = 30$), and between severe sepsis and septic shock study groups. In non-survivors testican-1 levels were significantly higher (63.37–151.85 ng mL^{-1}) than in survivors (3.17–9.77 ng mL^{-1}). The authors suggested that testican-1 could be used to diagnose and determine the severity of sepsis [27].

CHARACTERISTICS OF PRESEPSIN

The triggering of innate immune responses by pathogens and pathogen-associated molecular patterns (PAMPs) has been identified as an early and primary mechanism of sepsis. Immunity against a microorganism relies primarily on the activity of monocytes and macrophages that recognize PAMPs [28] partly via CD14, having an immediate response against lipopolysaccharides. The lipopolysaccharide-binding protein (LBP) and CD14 enhance the detection of LPS by the toll-like receptor 4 (TLR4)-myeloid differentiation factor 2 (MD-2)-complex by extracting and monomerizing LPS before its presentation to TLR4-MD-2 [29]. CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). mCD14 has a high affinity to LPS and is mostly expressed on monocytes/macrophages. sCD14 is produced by cell secretion or mCD14 fall-off. During activation and shedding of CD14 from the cell surface membrane, one molecule of sCD14 is split into approximately four molecules of the 13 kDa fragment. The N-terminal fragments of 13 kDa consist of sCD14 subtype (sCD14-ST) also called presepsin. sCD14 helps to mediate the immune response to LPS of CD14-negative cells such as epithelial and endothelial cells and is cleaved by cathepsin D and other proteases [30]. The sensitivity of presepsin is not significantly different between Gram-positive and Gram-negative bacterial infections. The level of presepsin could be elevated in fungal but not in virus infections. The distribution of presepsin values is different for healthy controls (294.2 ± 121.4 pg mL^{-1}) and septic patients (817.9 ± 572.7 pg mL^{-1}) [31]. The level of presepsin typically increases within 2 hours and reaches a peak in 3 hours after infection [32]. This evidence indicates that presepsin is a better biomarker for the early stage of sepsis than the later stage [33]. By using the chemiluminescence enzyme immunoassay as a detecting tool, the result can be available in 1.5 hours [34]. With improvement

in presepsin assay methods, presepsin may become a point-of-care tool for bedside diagnosis of sepsis in the future [35].

Role of presepsin in sepsis

Tong *et al*. [35] in a meta-analysis evaluated the diagnostic accuracy of presepsin in sepsis patients. 11 publications with 3106 patients were included in the meta-analysis and according to their results the pooled sensitivity was 0.83 (95% CI: 0.77–0.88), specificity was 0.81 (95% CI: 0.74–0.87), positive likelihood ratio was 4.43 (95% CI: 3.05–6.43), and negative likelihood ratio was 0.21 (95% CI: 0.14–0.30). The area under the curve (AUC) was 0.89 (95% CI: 0.86–0.92). Estimated for a sepsis spread of 20%, positive and negative post-probability values were 53% and 5%, respectively. The authors suggested that despite the important role of presepsin in sepsis diagnosis, its measurement should be connected with usually used biomarkers, such as procalcitonin, C-reactive protein and white blood cells. In this study the authors revealed that using presepsin there were relatively many missed or incorrect diagnoses and hence this indicator should be used in conjunction with procalcitonin, rather than replace PCT [35].

Endo *et al*. [36] in a multicenter prospective study compared the clinical utility of presepsin with PCT, IL-6 and CRP. 103 patients with sepsis admitted to the emergency room or ICU were included in the study and classified into 3 groups: sepsis, severe sepsis and septic shock. The patients were further divided into favorable and unfavorable prognosis groups on the basis of Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. The patients in the favorable prognosis group revealed a significant decrease in all biomarkers levels on days 3 and 7 after admission. In the unfavorable prognosis group, only presepsin levels did not decrease significantly during follow-up. The unfavorable prognosis group had significantly higher 28-day mortality than the favorable prognosis group ($P < 0.05$). The authors revealed that presepsin levels correlated with the severity of sepsis during follow-up in comparison with other sepsis biomarkers [36].

In a meta-analysis Wu *et al*. [37] assessed accuracy of presepsin in sepsis diagnosis and reported sensitivity of presepsin ranging from 0.71 to 1.00, specificity from 0.62 to 0.98, positive likelihood ratio from 1.71 to 39.75, negative likelihood ratio from 0.02 to 0.34, and diagnostic odds ratio from 6.09 to 2403.40; the pooled sensitivity of presepsin for sepsis was 0.78 (95% CI: 0.76–0.80), pooled specificity was 0.83 (95% CI: 0.80–0.85), pooled positive likelihood ratio was 4.63 (95% CI: 3.27–6.55), pooled negative likelihood ratio was 0.22 (95% CI: 0.16–0.30), and the AUC of the SROC curve was 0.89 (95% CI: 0.84–0.94). The authors concluded that presepsin might be a valuable biomarker in early diagnosis of sepsis but is not recommended as a definitive and only test for sepsis confirmation [37].

Yang *et al*. [38] in adult septic patients assessed in a meta-analysis the prognostic value of presepsin. Ten studies and 1617 patients were included. According to their results during the first 24 hours presepsin levels were significantly lower in survivors vs. non-survivors and the pooled standardized mean difference (SMD) between the groups was 0.92 (95% CI: 0.62 ± 1.22). Additionally, in subgroups, divided by the sepsis severity, pooled SMD for presepsin was significantly higher in non-survivors ($P < 0.05$). According to the authors' opinion, their results indicated some mortality prediction value of presepsin in patients with sepsis but defining the optimal cut-off point of presepsin requires further studies [38].

Matera *et al*. [39] in an observational, prospective study assessed 58 surgical and medical ICU patients with suspected sepsis. Taking into consideration the 28-day mortality and blood culture results the study group was retrospectively divided into survivor and non-survivor subgroups, and positive and negative microbiological result subgroups. The timing of plasma and serum collection was as follows: on admission (T-0), after 24–48 hours (T-1) and after 7 days (T-2). According to their results presepsin levels were significantly higher at T-0 ($P = 0.0007$), at T-1 ($P < 0.0001$) and at T-2 ($P < 0.0001$) in the non-survivor subgroup at the same time point. Additionally, presepsin concentrations were significantly higher at T-0 ($P = 0.0073$), T1 ($P = 0.0111$) and T2 ($P = 0.0167$) in patients with positive blood cultures. Results of multivariate analysis indicated that presepsin is an independent predictive variable among prognosis markers at T-0 ($P = 0.016$). Based on these results, the authors assessed presepsin as an interesting prognostic and diagnostic biomarker in patients with severe sepsis [39].

CHARACTERISTICS OF MID-REGIONAL PRO-ADRENOMEDULLIN

Adrenomedullin (ADM) was first discovered in human pheochromocytoma tissue in 1993 [40]. ADM is a 52 amino acid peptide representing the calcitonin gene-related peptide family. The ADM encoding gene consists of 4 exons and 3 introns and is located on chromosome 11. The gene is transcribed into a pre-messenger RNA (mRNA) molecule, containing 4 exons and 3 introns. The formation of a mature mRNA molecule, being translocated and processed into ADM, results from removal of all introns.

The expression of ADM concerns all tissues but the highest concentrations of the peptide are found in the adrenal medullae, cardiac atria and lungs. ADM exerts its effect after ligation of receptor complexes consisting of the calcitonin receptor-like receptor (CRLR) together with a specific receptor activity-modifying protein (RAMP) [41]. ADM receptors are expressed by blood vessels, skeletal muscles, heart, lungs, nerve tissues and on a cellular level by ECs, cardiomyocytes, vascular smooth muscle cells, macrophages and dendritic cells. Circulating ADM has a half-life of approximately 22 minutes and is degraded by protease [42]. ADM is classified as "hormokine", because of a hormone-like activity profile in non-inflammatory conditions when its only source is endocrine cells, and by a cytokine-like activity profile in sepsis when it is ubiquitously overexpressed [41]. Rapid degradation and clearance of circulating ADM complicates its measurement and quantification. The mid-regional fragment of pro-adrenomedullin (MR-proADM), including amino acids 45–92, is more stable and directly reflects levels of active ADM [43, 44].

Role of mid-regional fragment of pro-adrenomedullin in sepsis

The vascular endothelium is a protective barrier, and the inflammatory response in sepsis is characterized by endothelial cells' destruction resulting in loss of barrier integrity. Endothelial dysfunction is one of the most important septic pathological factors. Loss of barrier integrity is responsible for the edema, decreased blood pressure and subsequent organ failure observed in sepsis/septic shock. Adrenomedullin is a key hormone involved in regulation of the endothelial barrier and vascular tone [42].

ADM inhibits actin-myosin based endothelial cell contraction and junctional disassembly, thereby preventing paracellular permeability and edema formation. The peptide possesses several protective cardiovascular qualities, including protection of the microcirculation during inflammation, and it was proven that it could act as an endogenous immunomodulatory factor with predominant anti-inflammatory effects in various models of sepsis and septic shock [45, 46]. In an animal model of septic shock, Gonzales-Rey *et al*. [46] revealed that animals treated with ADM did not present any of the histopathological alterations associated with septic shock, such as disseminated intravascular coagulation, leukocyte infiltration, inflammation in various organs, and mesenteric ischemia, tissue congestion and hemorrhage. The authors confirmed that the administration of ADM reduced the levels of endotoxin-induced inflammatory cytokines (TNF-α, interferon gamma [IFNγ], IL-6, IL-1β and IL-12), the chemokines regulated upon activation normal T cell express sequence (RANTES) and macrophage inflammatory protein-2 (MIP-2) and nitric oxide (NO) in serum (systemic), and in various target organs, including peritoneum, liver, lung and intestine. According to their results, ADM administration increased the systemic and local levels of the anti-inflammatory cytokine IL-10 [46].

Elke *et al.* [47] performed a randomized controlled trial analysis in patients with severe sepsis or septic shock across 33 German ICUs. Patients were stratified into low, intermediate, and high severity groups and 1089 patients with a 28-day mortality rate of 26.9% were analyzed. According to the Sepsis-3 definition, 41.2% of patients fulfilled the criteria for sepsis and 58.8% for septic shock, with mortality rates of 20.0% and 32.1%, respectively. In their results MR-proADM revealed the strongest association with mortality across all subgroups and could facilitate a precise classification of low and high disease severity. Patients with continuously high MR-proADM levels but decreasing PCT levels had a significantly higher mortality risk. The authors concluded that MR-proADM is a more accurate disease severity and mortality risk stratification biomarker than clinically established biomarkers and scores. Changes in MR-proADM kinetics may be used to identify patients at risk of treatment failure despite ongoing antimicrobial therapy [47].

Enguix-Armada *et al*. [48] in a 388-patient cohort assessed whether the combination of CRP, PCT, presepsin and MR-proADM measured in the first 24 hours after ICU admission allows better management of septic patients. In their results PCT showed the highest AUC (0.989) as compared with the rest of the biomarkers ($P < 0.01$). PCT also enabled the difference between Gram-positive or Gram-negative bacteria to be determined. The AUCs for CRP (0.922) and presepsin (0.948) showed a similar diagnostic value. In cases of septic shock the AUC of presepsin revealed a significant increase ($P < 0.0001$). MR-proADM showed better prognostic value ($P = 0.00022$) particularly in cases of septic shock ($P = 0.00001$) increasing along with the APACHE-II score. The authors concluded that PCT, MR-proADM and presepsin, when they are measured in the first 24 hours after ICU admission, are complementary markers in the management of septic patients [48]. Mebazaa *et al*. assessed the relationship between circulating bio-adrenomedullin (bio-ADM-bioactive form of ADM) during the initial ICU stay, short-term outcomeand reversibility of organ failure in sepsis in the prospective observational multinational AdrenOSS-1 study. Circulating bio-ADM levels were measured upon admission and on day 2. Median bio-ADM concentration at admission was 80.5 pg/ml (IQR

41.5–148.1 pg mL^{-1}). The initial SOFA score was 7 (IQR 5–10), and 28-day mortality was 22%. An association was found between bio-ADM at admission and 28-day mortality (unadjusted standardized HR 2.3 [CI: 1.9–2.9]; adjusted HR 1.6 [CI: 1.1–2.5]) and between bio-ADM levels and SOFA score ($P < 0.0001$). In patients with bio-ADM > 70 pg mL^{-1} at admission, decrease in bio-ADM below 70 pg mL^{-1} at day 2 was associated with recovery of organ function at day 7 and better 28-day outcome (9.5% mortality). Constantly elevated bio-ADM at day 2 was linked to prolonged organ dysfunction and high 28-day mortality (38.1% mortality, HR = 4.9, 95% CI: 2.5–9.8) [49]. Preclinical work performed with the non-neutralizing ADM-binding antibody adrecizumab in animal models of septic shock revealed improved vascular barrier function, reduced vasopressor dosage and organ dysfunction and increased survival. Therapeutic use of adrecizumab possibly improves outcome patients with septic shock and high ADM plasma concentrations. There were no safety concerns in phase I studies in healthy volunteers. In a biomarker-guided trial, the safety and efficacy of adrecizumab will be assessed in patients with septic shock [50].

CONCLUSIONS

Due to the complexity of sepsis and the diversity of patient populations, it should be expected that combinations of biomarkers will be required to obtain more precise information on the effectiveness of the treatment. Biomarkers could offer better and more rapid stratification of patients in order to identify those who might benefit and require more advanced and targeted therapies. Future real-time measurements of biomarkers could identify the pathologic mechanism and direct therapeutic strategies in septic patients.

Recently, there have been increasing data indicating that kallistatin, testican-1, presepsin, and mid-regional pro-adrenomedullin or bio-ADM are promising biomarkers significant in diagnosis and monitoring of sepsis. According to animal model results, kallistatin and mid-regional pro-adrenomedullin, because of their protective and anti-inflammatory activity, are potential treatment options in sepsis/septic shock. The clinical usefulness of described biomarkers is still open to discussion and requires further studies.

ACKNOWLEDGEMENTS

1. Financial support and sponsorship: none.
2. Conflict of interest: none.

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