Markers and Mediators of Inflammatory Response in Infection and Sepsis*

Indicadores e Mediadores de Resposta Inflamatória na Infecção e Sepse

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RESUMO

JUSTIFICATIVA E OBJETIVOS: A sepse é a expressão de uma complexa rede de mediadores. Falência de múltiplos órgãos e choque séptico são as principais causas de óbito nas unidades de terapia intensiva em todo o mundo. Indicadores biológicos como as citocinas, bem como centenas de outros indicadores celulares, moléculas bioativas circulantes ou produtos da coagulação são potenciais indicadores biológicos que poderão ser de grande utilidade no reconhecimento e tratamento da infecção e sepse. O objetivo deste estudo foi apresentar os principais indicadores que podem ser utilizados, atualmente ou possivelmente, no futuro, na prática clínica ou experimental.

CONTEÚDO: Revisão dirigida da literatura sobre possíveis indicadores de infecção e sepse, com ênfase aos da cascata da coagulação, proteína C-reativa e procalcitonina.

CONCLUSÕES: O papel da maioria dos indicadores biológicos não está ainda definido para uso na prática clínica. Todavia os níveis séricos de PCR e de procalcitonina podem ser de grande auxílio no diagnóstico e no prognóstico da infecção e da sepse quando usados em conjunto com os parâmetros convencionais.

Unitermos: choque séptico, falência de múltiplos órgãos, indicadores, mediadores, sepse, síndrome da resposta inflamatória sistêmica.

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SUMMARY

BACKGROUND AND OBJECTIVES: Sepsis is the expression of a complex network of mediators. Multiple organ dysfunction and septic shock indeed remain a major cause of death among ICU patients worldwide. Prompt recognition of both the diagnosis and the complicated evolution are essential, hence the importance of using biological markers. The main pro-inflammatory and anti-inflammatory cytokines as well as hundreds of others cellular markers, circulating bioactive molecules or coagulation products are potential biological markers that could help to characterize the presence of infection and sepsis. We aimed to review the main biological markers that could be used nowadays or possibly in the future, either in clinical or research fields.

CONTENTS: A selective review of biologic markers of sepsis focusing on markers of the coagulation cascade, C-reactive protein and procalcitonin.

CONCLUSIONS: Most of the available biological markers is still not a practical method to be used at the bed-side and is currently restricted to research works. Nowadays the determination of CRP or PCT serum levels can be of great help in the critically ill patient care along with the conventional parameters.

Key Words: markers, mediators, multiple organ dysfunction, sepsis, septic shock, systemic inflammatory response syndrome.

INTRODUCTION

It is often very difficult to distinguish infection, which is a microbiological process, from sepsis that is the host reaction to this process. As many as 1 million patients

develop severe sepsis annually in US and more than 300,000 require organ support[1]. Septic shock indeed remains a major cause of death. Therefore, prompt recognition of both the diagnosis and the severity of the disease are essential. The main pro-inflammatory and anti-inflammatory cytokines as well as lots of other cellular markers, bioactive circulating molecules or co-agulation products are potential biological markers that could help to distinguish the presence of systemic inflammatory response syndrome (SIRS), disseminated intravascular coagulation (DIC) and sepsis[2]. We aimed to review the main biological markers that could be used nowadays or possibly in the future, either in clinical or research fields.

BIOLOGICAL MARKERS

In a simplified way, in sepsis, the mononuclear pha-gocytes bind to microbial structures through receptors such as CD14 and Toll-like, signaling for the produc-tion of some mediators, dependent on the activation of nuclear factor-κB genes[2,3]. Toll-like receptors (TLR) are transmembrane proteins that interact with different agents[4]. The most known are the TLR4 that interacts with the endotoxin; the TLR2 that interacts with the components of the cellular membrane of the gram-po-sitive bacteria; the TLR5 whose ligand is the flagellin, the main protein component of the flagella of bacteria, and the TLR3 for the virus. Efforts have been made in understanding the signaling mechanisms of TLR. Inhi-bition of TLR and proinflammatory cytokine signaling highlights new ways for future treatments.

There are other receptors that recognize the lypopoly-saccharide (LPS), such as CD11/CD18, K^+ channels and macrophage scavenger receptor. Other soluble and membrane proteins are involved in the recognition of bacteria and its products, such as protein recognition peptidoglicans and triggering receptor expressed on myeloid cells (TREM-1)[5]. TREM-1 may be a potential therapeutic target for septic shock. The determination of the level of a soluble form of TREM-1 (sTREM1) rele-ased from the activated macrophages in biological flui-ds as plasma or bronchoalveolar lavage help to rapidly identify the presence of infection[6].

Some cytokines are earlier released during the inflam-matory response; interleukin-1 (IL-1) and the tumor necrosis factor-α (TNF). It is followed by the produc-tion of other pro-inflammatory cytokines, such as IL-6, IL-8; and anti-inflammatory, such as soluble IL-10 and its receptors (IL-2r, TNF55r and TNF75r)[2,3]. Both the IL-

6 and the TNF-α induce the synthesis of acute phase proteins, particularly C-reactive protein (CRP) and the procalcitonin (PCT)[7]. The extreme and prolonged incre-ase of IL-6 circulating level after trauma, burning, SIRS, sepsis and elective surgery is related to morbidity and mortality[8,9]. After major surgery, a raised IL-6 level in day 1, when associated with signs of SIRS, is an ear-ly marker of sepsis[10]. An up-regulation of inflammatory cytokines production was reported in the earliest stage of sepsis followed by dramatic down-regulation in the phases of severe sepsis or septic shock[11].

An important cytokine protein is the macrophage migra-tion-inhibitory factor (MIF). The MIF plays a role in the modulation of immune response through TLR4 allowing the prompt macrophage response. High levels of MIF have been detected in patients with severe sepsis and septic shock and were associated with microbiologi-cally documented sepsis after cardiac surgery[12,13]. Ano-ther mediator, pre-B-cell colony-enhancing factor may be required for complete expression of the thrombin-induced inflammatory response and has the potential to be a novel marker of acute lung injury and endothe-lial barrier dysfunction[14]. A protein known as HMGB1 (High Mobility Group Box-1) has been described as a late mediator of inflammation and sepsis. Patients with sepsis have a high concentration of HMGB 1 up to 1 wk after admission[15].

COAGULATION MARKERS

The systemic inflammation is followed by the coagu-lation system activation[16]. Figure 1 represents the in-teraction between inflammation and coagulation. The endothelial injury caused by LPS and pro-inflammatory cytokines stimulates the production of the tissue fac-tor (TF). The excessive production of thrombin and its inadequate removal by the fibrinolytic system result in widespread intravascular deposition of fibrin characte-rizing DIC. Routine blood tests do not have the neces-sary specificity for DIC diagnosis[17]. DIC dynamics may be better evaluated by measuring markers of the coa-gulation activation or the secondary fibrinolysis, such as prothrombin fragment 1+2 (F1+2), antithrombin (AT), soluble fibrin (SF), thrombin-antithrombin complex (TAT), and fibrin degradation products (FDP)[18,19].

The beginning of sepsis is marked by an immediate de-cline in the activity of factor VIIa followed by a gradual increase in the plasma levels of F1+2 and complex TAT; direct evidence of pro-coagulant state[20]. However, the specificity of F1+2 for DIC is low once the coagulation
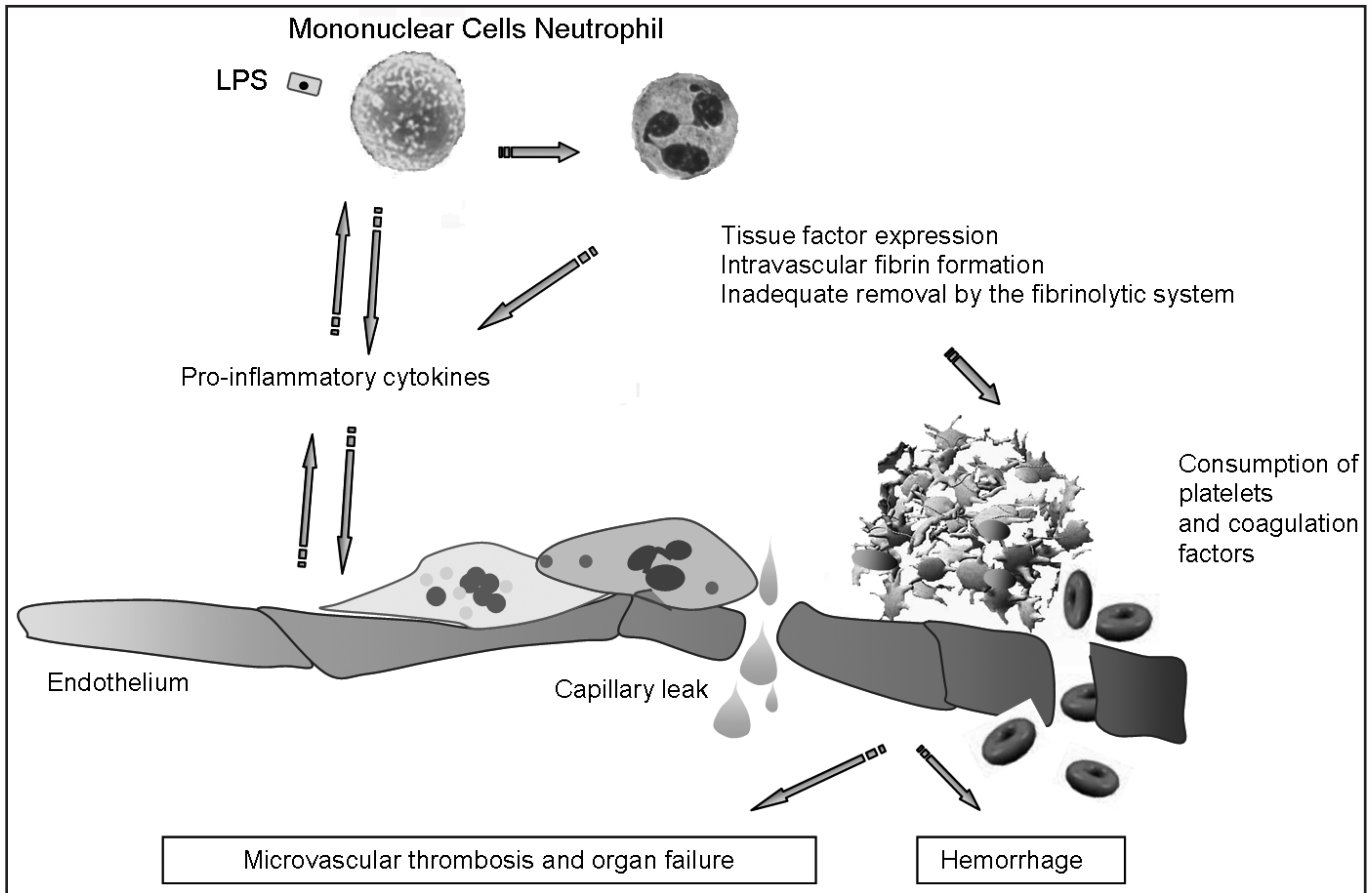
Figure 1 - Schematic Representation of the Interaction between Inflammation and Coagulation.

process can also be triggered in the extravascular space in the absence of DIC, as in trauma or pancreatitis[21]. The plasma levels of TAT are high in the majority of patients with sepsis even in the absence of clinical signs of DIC, and it is related to multiple organ dysfunction (MOD), shock and death[22]. The TAT high sensitivity can be useful to detect coagulation activation, even at slight degrees; nevertheless its specificity is limited once increased TAT serum levels can also appear in other clinical situations such as venous thromboembolism.

The initial fibrin formation product will be a complex of fibrin monomer with two fibrinogen molecules that will aggregate more molecules and will become insoluble. Thus, it consists of a variety of complexes such as the fibrin-fibrinogen trimolecular complex, the fibrin-FDP complexes, the fibrin-factor XIIIa complexes, and others. The SF is an indicator of continuous intravascular coagulation process once it is only produced in intravascular medium, and remains in circulation for many hours[23]. It was showed a high sensitivity of SF for DIC diagnosis in neurosurgical and critically ill patients[24].

When fibrinogen is converted into fibrin by thrombin, a systemic fibrinolytic, plasmin, cleaves the fibrinogen/fibrin of thrombus originating its degradation products. The D-dimer is a specific test for fibrin degradation products. However, high D-dimer serum levels are also found in many clinical situations, such as deep venous thrombosis and pulmonary thromboembolism[25]. A negative serum test for FDP does not exclude the diagnosis of DIC. But in severe sepsis changes in D-dimer serum concentration was an independent predictor of death[20]. On the other hand, the plasma levels of coagulation natural inhibitors, such as AT and protein C are remarkably reduced in sepsis and septic shock with or without signs of DIC[18,26]. Mortality rates of 90-100% are described in surgical and septic patients after trauma with AT lower than 70% and 60%, respectively[27]. A reduced AT serum level is a predictor of infection or complicated course in polytraumatized patients[28]. The presence of an AT lower than 54% in the first day of severe sepsis was an independent predictor of death[20]. In severe sepsis more than 80% of the patients have reduced protein C levels. The protein C plasma levels are inversely correlated to mortality[29].

Up to date, the available tests do not present the necessary specificity for their routine use. Therefore, in the absence of a gold standard the diagnosis of DIC is based on a combination of an appropriate clinical entity known to be associated with DIC, the presence of clinical manifestations, mainly organ dysfunction, and laboratory markers of deranged clotting, such as prolonged clotting times (activated partial thromboplastin time, prothrombin time), and reduced levels of fibrinogen and platelets, and if available an abnormal test for activated clotting such as fibrin degradation products[17]. Other more complex tests are available only in specialized laboratories.

C-REACTIVE PROTEIN

Significant rises in CRP serum concentrations are observed in invasive infections, caused by gram-positive and gram-negative bacteria, as well as systemic fungal infections even in immunodeficient patients[30]. In contrast, lower increases are observed in acute viral infections. The value of a single CRP measurement in the diagnosis of infection and sepsis was investigated in some studies. It has been show that CRP is an excellent infection marker in patients admitted in the emergency room with a cut-off level of 6 mg/dL (sensitivity = 67%, specificity = 94% and a ROC curve of 0.88)[29]. On hospital admission, plasma levels of CRP have been over 5 mg/dL in all the patients with community-acquired pneumonia (CAP), and over 10 mg/dL in 75%[32]. CRP serum level is the best predictor of positive cultures after aspirative bronchopneumonia and higher levels are found in patients with pneumonia than in patients with infected bronchitis[33]. Patients presenting maximum daily CRP variation > 4.1 mg/dL plus a CRP level > 8.7 mg/dL had an 88% risk of infection[34]. In the first 24 hours decreases of CRP over 20% is independently associated with survival and are indicative of infection resolution[35,36].

Discrete increases in CRP serum concentrations are associated with cardiovascular disease, systemic lupus erythematosus, dermatomyositis, systemic sclerosis, graft versus host disease, and leukemia[37,38]. However, in response to the infection, these patients are still capable of raising their CRP, distinguishing infection from disease relapse. Significant raises are still observed in major burning, acute pancreatitis and cancer[30]. In these conditions the persistence of high levels has suggested a complicated course and a second increase is highly suggestive of an infectious complication.

CRP serum levels between 5-10 mg/dL have been suggested as cut-off point for diagnosis of sepsis with sensitivity ranging from 71.8% to 98.5%, and specificity ranging from 47.5% to 75%[39,40]. High levels of CRP can indicate an evolution with organ dysfunction. In a heterogeneous group of critically ill patients the presence of high concentrations of CRP is related to the presence of organ dysfunction, necessity of dialysis therapy, higher ICU length of stay, and high rates of infection and mortality[41]. Higher CRP concentrations (10 mg/dL) at admission were associated to a particularly raised mortality. A fast decrease was associated to a more favorable evolution.

The differential diagnosis between graft rejection and sepsis is frequently difficult after organ transplants. The CRP serum levels raises just after liver transplant and reaches the maximum peak in the second day. The maximum CRP levels observed in patients with graft rejection remain low in comparison with increased CRP levels in those with infectious complications[42]. After bone marrow transplant CRP peak was the best independent predictor of a complicated evolution[43].

CRP has negative prognostic value in critically ill patients. Elderly critically ill patients who have not survived presented average CRP serum concentrations at ICU admission significantly higher than the survivors[44]. A good correlation was reported between CRP and two prognostic scores - MPM II (Mortality Predict Model) and APACHE III score[45]. The dynamic serial evaluation of CRP levels is a valuable tool in the diagnosis and follow-up of critically ill patients and can be of great help in the decision of further procedures such as culture sampling, radiology exams or the re-adequacy of antibiotic therapy.

Procalcitonin
The use of PCT as an infection marker has been studied especially in newborn and children, in whom the infection diagnosis is more difficult[46]. Slight increases in PCT serum concentrations occur in local bacterial and viral infections besides other conditions as uremia, cardiogenic shock, noninfectious chronic inflammatory processes and neoplastic diseases[47]. Important increases of PCT are observed in systemic bacterial infections, bacterial meningitis, peritonitis, and septic shock.

In a heterogeneous group of critically ill patients a cutoff point of 0.6 ng/mL for PCT was described for the diagnosis of infection[40]. However, in elderly patients high levels might not be indicative of infection[48]. A randomized trial investigating guidance of antibiotic treatment

duration in CAP by procalcitonin test markedly reduced antibiotic exposure in patients with CAP by reducing the duration of therapy from a median of 12 to 5 days[49]. This finding might have enormous implications in clinical practice.

In community-acquired bacterial meningitis a significant decrease in serum PCT was associated with cure[50]. PCT serum levels of 1.3 ± 0.2 ng/mL, 2 ± 0 ng/mL, 8.7 ± 2.5 ng/mL and 38.6 ± 5.9 ng/mL were reported respectively for SIRS, sepsis, severe sepsis and septic shock[47].

The behavior of the PCT plasma concentrations in patients with acute renal failure is still not well known. However, PCT is better related to the severity of complications in cardiac surgery and trauma patients than CRP[51,52].

CONCLUSION

The dosage of the majority of the biological markers is not yet a practical method to be used. Although many markers can identify patients at risk of infection, risk of organ dysfunction, renal failure and other outcomes whether they can be used to guide clinical decisions is not yet very clear. To date sepsis remains a clinical diagnosis. Nevertheless, at the moment, either PCT or the CRP are good markers of infection and sepsis and should be used judiciously to help decisions in the critically ill patient care along with the conventional parameters. Daily, sequential measurement of inflammatory markers is of much more value to guide therapy. Particularities of the two tests should be taken into consideration. Coagulation markers and sTREM-1 seem to be promising tools to help the management of sepsis.

Abbreviators

TLR -Toll-like receptors
TREM-1 - triggering receptor expressed on myeloid cells
IL – interleukin
TNF - tumor necrosis factor-α
CRP - C-reactive protein
PCT – PCT
MIF- macrophage migration-inhibitory factor
High Mobility Group Box-1- HMGB1
TF- tissue factor
F1+2 - prothrombin fragment 1+2
AT – antithrombin
SF - soluble fibrin
TAT - thrombin-antithrombin complex
FDP - fibrin degradation products

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