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Biomarkers in polytrauma induced systemic inflammatory response syndrome and sepsis – a narrative review

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Abstract

Polytrauma still represents one of the leading causes of death in the first four decades of life. Septic complications represent the predominant causes of late death in polytrauma patients. Early diagnosis and treatment of infection is associated with an improved clinical outcome and reduced mortality. Several biomarkers have been evaluated for making early diagnosis of sepsis. Current evidence does not support the use of a single biomarker in diagnosing septic complications. Procalcitonin trend was found to be useful in early identification of post-traumatic sepsis.

Key words: cytokine, multiple trauma, systemic inflammatory response syndrome, sepsis

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Introduction

Multiple trauma is a significant cause for morbidity and mortality, being the most frequent cause of death in young patients [1]. Trauma remains the leading cause of death in the world in patients under 45 years of age.

Hypoxia, hypovolemia and severe organ injuries represent immediate, direct causes for trauma mortality in the first few hours following the injury. Homeostatic physiologic responses that try to limit the injury imply the activation of immune cells function, the local and systemic release of pro and anti-inflammatory mediators, the activation of the coagulation cascade and the complement systems. Early after extensive trauma, the excessive activation of these immunologic responses leads to the development of the systemic inflammatory response syndrome (SIRS). The initial proinflammatory response is followed by the anti-inflammatory response syndrome, which implies immune suppression and a high risk towards the development of severe infection and sepsis [2]. Late after trauma, sepsis represents the most frequent cause of death [3].

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Sepsis and systemic inflammation immune biomarkers

The systemic inflammatory syndrome, as well as sepsis, imply the activation of immune cells' function (neutrophils, monocytes, macrophages, lymphocytes, endotelial cells, natural killers cells), the activation of the coagulation cascade and the fibrinolitic systems, the synthesis of mediators like stress hormones (ACTH, cortisol, cathecolamines), histamine, kinines, arachidonic acid derivatives (leukotrienes, prostaglandines and thromboxane), cytokines and chemokines, followed by the systemic release and the subsequent progression towards multiple organ dysfunction syndrome (MODS), with a high lethal risk [4-6]. In the first days after trauma, MODS development is associated with the systemic inflammatory response syndrome and a proinflammatory state mediated by T helper 1 lymphocytes (Th-1). Several days after trauma, MODS development is associated with sepsis due to the immune suppression induced by the anti-inflammatory immune response mediated by T helper 2 lymphocytes (Th-2) [2]. The differentiation between SIRS and sepsis is difficult, both being clinically expressed through nonspecific signs such as fever, leukocytosis, tachy-

cardia and tachypnea [7], while the bacteriologic results are often late and it is frequently difficult to differentiate colonisation from infection [8]. Delay in the diagnosis and initiation of antibiotics have been shown to increase mortality [7].

The proinflammatory mediators are: interleukine-1 (IL-1), interleukine-2 (IL-2), tumoral necrosis factor - alpha (TNFα), interleukine-6 (IL-6), interleukine-12 (IL-12), interferon gamma (IFNγ) (Table 1). These mediators are released by immune cells such as mono-

Table 1. Biomarkers of pro and anti-inflammatory responses, their origin and main functions *in vivo*

Mediator	Function	Origin	Immune effects
IL-1	proinflammatory	monocytes, macrophages, endothelial cells	Increases capillary permeability, activates coagulation, induces fever and haematopoiesis, activates lymphocytes and macrophages, stimulates the release of TNFα and other mediators
IL-2	proinflammatory	T lymphocytes	IL-2 is necessary for the growth, proliferation and differentiation of T cells to become 'effector' T cells IL 2 facilitates the production of immunoglobulins made by B cells and induce the differentiation and proliferation of natural killer cells.
IL-6	pro and antiinflammatory	macrophages, monocytes, T lymphocytes	Controls lymphocytes differentiation, activates neutrophils and NK cells, mediates the synthesis of acute phase proteins in the liver, induces fever.
IL-12	proinflammatory	monocytes, macrophages	Lymphocyte differentiation towards Th-1 line
IL-8	proinflammatory	macrophages, monocytes	Important role in chemotaxis, controls the migration of immune cells.
IL-4	antiinflammatory	monocytes	Immune protection and defence
IL-10	antiinflammatory	mononuclear blood cells	T lymphocytes inhibition and immune supression
IL-17	proinflammatory	T-helper cells induced by IL-23	Acts as a potent mediator in delayed-type reactions by increasing chemokine production in various tissues, in order to recruit monocytes and neutrophils to the site of inflammation and is similar to Interferon gamma.
IL-13	antiinflammatory	T helper type 2 (Th2) cells	Immune protection and defence
TNFα	proinflammatory	macrophages, monocytes, T lymphocytes	Immune cells activation, nitric oxide synthesis, activates arachidonic acid derivatives and other mediators (IL-6, IL-8, IL-10, IFNγ) synthesis.
IFNγ	proinflammatory	macrophages, T lymphocytes	Macrophages and neutrophils function activation, induces the synthesis of TNFα.
TGF-β	antiinflammatory	TGF-beta is secreted by many cell types, including macrophages	Limits T lymphocytes, macrophages and neutrophils responses.
C3a, C5a	proinflamatory	C3a and C5a anaphylatoxins are cytokine-like polypeptides generated during complement (C) system activation and released at the inflammatory site	Increase capillary permeability by inducing histamine release. Increases neutrophils chemotaxis, bacterial opsonisation, platelet activation.
PCT	proinflammatory	Immune and somatic cells including adypocytes	Biomarker for bacterial infection and sepsis.
NT-CNP	proinflammatory	Endothelial cells	Sepsis-related vasodilatation, potential useful biomarker for sepsis.
PCR	proinflammatory	Acute phase protein synthetised in lungs and liver	Nonspecific inflammation marker (trauma, burns, sepsis, autoimmune diseases). Influences complement system function, opsonisation and phagocytosis.
Leukotrienes Prostaglandines Thromboxane	pro and antiinmflamatory	Arachidonic acid in cell membrane	Vascular tone modulation, vascular permeability, cell chemotaxis, the synthesis of cytokines and antibodies, lymphocytes' differentiation. PGE-2 inhibits TNFα and IL-12 production.
GM-CSF	proinflammatory	macrophages, T cells, mast cells, NK cells, endothelial cells, fibroblasts.	Stimulates stem cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes. Monocytes exit the circulation and migrate into tissue, whereupon they mature into macrophages and dendritic cells

Corroborated data [2, 3, 10, 12] IL-1 = interleukine 1; IL-2 = interleukine 2; IL-6 = interleukine 6; IL-12 = interleukine 12; IL-4 = interleukine 4; IL-8 = interleukine 8; IL-10 = interleukine 10; IL-17 = interleukine 17; IL-13 = interleukine 13; TNFα = tumor necrosis factor alpha; IFNγ = interferon gamma; TGF-β = transforming growth factor beta; C3a, C5a = complement components; PCT = procalcitonin; NT-CNP = N-terminal C natriuretic peptide; CRP = C-reactive protein; GM-CSF = granulocytes and monocytes colony stimulating factor

cytes, macrophages and T helper-1 lymphocytes [2]. The C3a and C5a complement components play an important role in the initiation and progression of inflammation. Pro and anti-inflammatory mediators balance influence survival rates [9]. High plasmatic proinflammatory mediators concentrations correlate with the systemic inflammation severity. In critically ill septic patients, low levels of proinflammatory biomarkers and high levels of anti-inflammatory mediators are associated with immune suppression and are predictors of a poor prognosis [9]. Exaggerated pro and anti-inflammatory responses may lead to MODS and death [10, 11].

Inflammatory biomarkers kinetics

The initial systemic inflammatory response in trauma is associated with the identification of systemic circulating biomarkers, each having a different activation profile, different timing for the peak effects and different clearance rates. Quantifying the inflammatory status through the identification of inflammation mediators has been tried in several studies. [13-17].

IL-1 and TNFα reach peak values immediately after trauma and have rapid plasma clearances, being eliminated in the first 24 hours (Fig. 1). IL-6 reaches peak values on the first day after injury and its plasma concentrations decreases gradually, reaching almost 0 on day 14 [16]. PCT shows peak values in the first 3-6 hours postinjury, then gradually decreases and its value has a second peak on day 7, decreasing afterwards by 30%/day until day 14 [16]. CRP plasma concentration increases gradually after trauma and presents the peak effects on days 3-6, afterwards its plasma value decreases slowly reaching 80% of the peak value on day 14 [16].

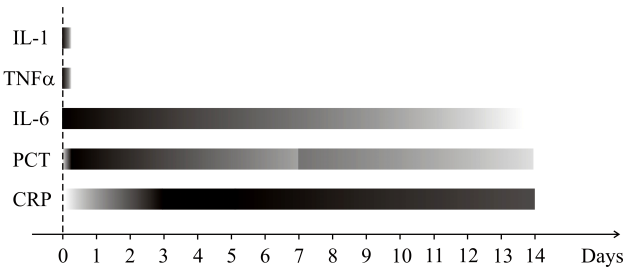

Fig. 1. Biomarkers plasma concentrations profile in patients with multiple trauma-induced systemic inflammatory response syndrome. IL-1 = interleukine 1; IL-6 = interleukine 6; TNFα = tumoral necrosis factor alpha; PCT = procalcitonin; CRP = C-reactive protein. Plasma concentrations are expressed in grey-scale as a colour gradient, peak concentrations being represented as black

SIRS-sepsis differential diagnosis

Biomarkers are substances that can be determined in the systemic circulation and their plasma concentrations dosing reflects physiological or pathological states such as systemic inflammatory response syndrome and sepsis [18].

The great majority of immune biomarkers released in pro and anti-inflammatory states belong to both SIRS and sepsis, but their different plasma profiles with changes in concentrations after systemic release or plasma clearance and their different kinetics could potentially differentiate between the two conditions and make room for specific treatments. Sepsis mortality in multiple trauma patients reaches 40% [6]. Early detection of sepsis by biomarkers dosing would draw attention towards bacteriological sampling and the commencement of empiric antibiotic treatment. Biomarkers concentration dosing could identify the patients with a favorable response to treatment and those who need treatment amendments.

In order to be clinically relevant, biomarker dosing needs good sensitivities and specificities [7]. To calculate sensitivity and specificity, the specific threshold value has to be adequately identified, though in previous studies several different cut-offs have been used for the same biomarker. Moreover, the clinician has to consider coexisting diseases and the time lapse from the time of injury to that of the laboratory *in vitro* dosing. The biomarker with absolute diagnostic value has not yet been identified, though over 3300 studies concerning 180 biomarkers have been performed [3, 7].

PCT and CRP are frequently used as SIRS and sepsis biomarkers. Their plasma concentration trend is similar in these two states, but with higher levels in sepsis [8].

For the time-being, procalcitonin (PCT) is the most studied and used biomarker. It is a precursor of the hormone calcitonin and is synthesized physiologically by tiroid C cells. In normal physiological conditions, PCT levels in the serum are low (< 0.1 ng/ml). In bacterial infection PCT is synthesized in various extra-thyroidal neuroendocrine tissues. Serum PCT levels start to rise at 4 h after the onset of systemic infection, and peak at between 8 and 24 h. It has the ability to identify severe bacterial infections and related sepsis [3, 7, 8]. PCT plasma values correlate with the severity of organ dysfunction and its decrease in the first day after the initiation of antibiotic treatment is a good predictor for the treatment efficacy. Immediately after trauma, the PCT plasma concentration is elevated, and the persistence of high values suggest the development of sepsis [7, 8, 16].

Until the wide use of PCT, CRP was the most extensively studied and used inflammation marker [3,

7]. Its sensitivity and specificity are lower than those of PCT. CRP plasma concentration increases slower, peaks at 36 h, when compared to PCT and the plasma clearance is similarly slower [8]. The decrease of the CRP values in five days after the initiation of antibiotic treatment is associated with good prognosis in septic patients [19].

IL-6 is produced and detectable within an hour after trauma. IL-6 presents increased values in both SIRS and sepsis, with higher values in septic shock [20].

None of the available biomarkers has absolute diagnostic value for multiple trauma-induced SIRS or the associated sepsis, although over 10 biomarkers have been studied [3]. Each biomarker has a different sensitivity and specificity for the identification of sepsis [8, 21-23], but their combined use might have a better diagnostic value, a hypothesis that deserves attention [3].

The prognostic value of some of the biomarkers has been addressed. PCT and IL-6 are associated with injury severity, the progression towards MODS and sepsis [17, 24-27], though their prognostic value is still debatable [24, 28]. IL-6 plasma concentration correlates well with the prognosis [2, 16, 29-32]. High PCT plasma values in the first five days after trauma are related to the development of sepsis [16]. High PCT values may be present even 3 days before the clinical identification of sepsis [33].

PCT, CRP and IL-6 show higher initial values in multiple trauma victims who progress later on to severe infections and sepsis [8, 16, 34], thus may be used as prognostic markers for infectious complications. PCT and IL-6 have their plasma peaks within the first 48 hours after injury and their levels decrease afterwards, while CRP plasma concentrations and leukocytes counts increase slowly and do not allow the differentiation of SIRS from sepsis [16]. To predict the development of sepsis, PCT seems to have a better prediction value when compared to IL-6 [33].

IL-10 has increased values in patients with sepsis and this represents a risk factor of mortality [9].

Currently available biomarkers seem to be up-regulated in SIRS of both septic and non-septic origin. Further research is needed to investigate which of them discriminates first between septic and non-septic trauma patients. Current evidence does not support the use of a single biomarker in diagnosing sepsis in trauma patients. More recently described cytokines, like IL 6, might bring additional diagnostic and prognostic information and need further evaluation in studies including a high number of trauma patients.

Conflict of interest

Nothing to declare

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Biomarkerii în cadrul sindromului de răspuns inflamator sistemic indus de politraumă şi sepsis – o actualizare

Rezumat

Politrauma continuă să reprezinte una din principalele cauze de deces în primele patru decenii de viaţă. Complicaţiile septice reprezintă cauzele preponderente de deces tardiv în cazul pacienţilor politraumatizaţi. Diagnosticul precoce şi tratamentul infecţiei este asociat cu o evoluţie clinică favorabilă şi o mortalitate redusă. Diferiţi biomarkeri au fost evaluaţi în scopul diagnosticului precoce al sepsisului. Indiciile actuale nu susţin un anume biomarker pentru diagnosticul complicaţiilor septice. Opţiunea pentru procalcitonină s-a dovedit utilă ca element de diagnosticare precoce a sepsisului posttraumatic.

Cuvinte cheie: citokine, politraumă, sindromul de răspuns inflamator sistemic, sepsis