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Jacobs Journal of Biomarkers

Research Article

Review of the Literature: Sepsis and Neutrophil Cd64

Silvana Teixeira Dal Ponte*[1], Ana Alegretti[2], Gabriela Petitot Rezende[3], Giordanna Andrioli[1], Luciano Diogo[1], Luciano Zubaran Goldani[4], Pauline Simas Machado[3], Renato Seligman[5]

[1]*Emergency physician, Department of Emergency, HCPA, Porto Alegre, Brazil*

[2]*Biochemistry pharmacist, Department of Clinic Pathology, HCPA, Porto Alegre, Brazil*

[3]*Medical student, Federal University of Rio Grande do Sul, HCPA, Porto Alegre, Brazil*

[4]*Infectologist, Head of Department of Infectology, HCPA, Porto Alegre, Brazil*

[5]*Pneumologist, Head of Department of Internal Medicine, HCPA, Porto Alegre, Brazil*

**Corresponding author: Dr. Silvana Teixeira Dal Ponte, Department of Emergency, : 60/600, Mário Leitão St, Porto Alegre, Brazil,*

Tel: +55 51 99449922; Email: sildalponte@gmail.com

Received: 06-23-2015

Accepted: 08-17-2015

Published: 08-25-2015

Abstract

Sepsis is a systemic inflammatory response against suspected or documented infection. In an infectious process, inflammation is triggered activating leukocytes, mainly neutrophils. CD64 is a surface antigen weakly expressed on non-activated mature neutrophils. When neutrophil CD64 is strongly expressed on neutrophils, it means neutrophils were activated, thus suggesting the presence of bacterial infection or acute fungal infection. A large number of biological substances has been investigated as candidate biomarkers and/or mediators of sepsis. Recent studies have focused on the investigation of neutrophil CD64 as a possible biomarker for the diagnosis of sepsis.

Keywords: Sepsis; SIRS; CD64; Biomarker

Abbreviations

CARS: Compensatory Anti-Inflammatory Response Syndrome;

CI: Confidence Interval;

CRP: C-Reactive Protein;

DBP: Diastolic Blood Pressure;

DIC: Disseminated Intravascular Coagulation;

EPCR: Endothelial Protein C Receptor;

HMGB-1: High-Mobility Group Protein B1;

ICU: Intensive Care Unit;

IL: Interleukin;

LPS: Lipopolysaccharides;

MODS: Multiple Organ Dysfunction Syndrome;

NLM: National Library of Medicine;

NOD: Nucleotide-Binding Oligomerization Domain;

PAI-1: Plasminogen Activator Inhibitor-1;

PAMPs: Pathogen-Associated Molecular Patterns;

PRRs: Pattern Recognition Receptors;

RNA: Ribonucleic Acid;

SBP: Systolic Blood Pressure;

SIRS: Systemic Inflammatory Response Syndrome;

TFPI: Tissue Factor Pathway Inhibitor;

TLRs: Toll-Like Receptors;

TNF: Tumor Necrosis Factor;

TREM-1: Triggering Receptors Expressed on Myeloid Cells

Concept

The inflammatory process is a normal response to trauma, infection, or injury. Inflammation may present as a local or systemic manifestation. The systemic inflammatory response syndrome (SIRS) is a complex pathophysiological response to different types of injuries. Its main complication is the multiple organ dysfunction syndrome (MODS), a condition showing high rates of mortality [1].

The concept of SIRS was defined at a conference of the American College of Chest Physicians and the Society of Critical Care Medicine in August 1992 in Chicago [1]. The purpose of this definition was to develop parameters that were easily applicable and widely available in clinical settings, making it possible to establish early diagnosis and to identify potential candidates for the evaluation of new treatments for sepsis [2]. Therefore, the definition of SIRS covers basic clinical and laboratory abnormalities. SIRS is diagnosed when two or more of the following criteria are detected: fever or hypothermia (body temperature > 38°C or < °36C); respiratory rate > 20 breaths per minute (tachypnea) or arterial partial pressure of CO_2 < 32 mmHg; heart rate > 90 bpm; significant increase or decrease in the number of leukocytes in peripheral blood (> 12,000 or < 4,000 cells/mm^3) or presence of more than 10% (> 500) immature bands [1]. Despite the fact that these criteria have been determined by consensus, there have been criticisms about their high sensitivity and low specificity, covering clinical conditions with different prognosis [3].

Specific terms and definitions related to infections have been used to facilitate communication. Therefore, microbial infection consists of an inflammatory response triggered by the presence of microorganisms or invasion of previously sterile tissue; bacteremia is the presence of bacteria in the blood [4]; and sepsis is a systemic inflammatory response against suspected or documented infection, showing the same manifestations defined for SIRS, but not limited to them [5]. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. Sepsis-induced hypotension is the presence of systolic blood pressure (SBP) < 90 mmHg or diastolic blood pressure (DBP) < 70 mmHg or a decrease in SBP of more than 40 mmHg or more than two standard deviations below baseline for age in the absence of other causes of hypotension. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is related to infection-induced hypotension with increased lactate and oliguria [6].

The fact that the criteria used to define SIRS are too sensitive, including even non-infectious diseases that do not involve inflammation, has been criticized. However, a study has shown that the larger the number of criteria of SIRS met by patients, the higher the mortality rate [7]. In addition, because it is an easy-to-apply concept, the definition of SIRS seems to be suitable for early diagnosis and treatment of this syndrome. Furthermore, there seems to be an increase in the number of studies involving SIRS and sepsis [3,8].

Attempting to avoid the progression to MODS, performing an early diagnosis is essential in order to establish the treatment as soon as possible. Focusing on this objective, many biomarkers have been studied. One of them is CD64, which has presented promising results.

The biomarker CD64 is expressed on activated neutrophils in inflammatory and infectious responses. The CD64 index is increased in patients with SIRS, sepsis and severe sepsis. It has a variable quantitative expression, which can be measured and analysed by specificity and sensibility. The CD64 index can be used to an early diagnosis of SIRS and sepsis and to determine the severity of the cases. In doing that, it is possible to streamline the diagnosis and target the treatment, improving the prognosis.

Epidemiology

The epidemiology of SIRS is rarely reported. Among the few existing studies, Horeczko et al. conducted a four-year study involving adult patients seen at emergency departments of U.S. hospitals and found that 17.8% of these patients had SIRS [9]. Another study investigated a sample of 3,708 patients and found a mortality rate of 7% of SIRS without sepsis, i.e., SIRS with no infectious cause [10].

Research involving epidemiological data on sepsis is more common. In general, sepsis occurs in about 2% of all hospitalizations in developed countries. Sepsis may affect between 6 and 30% of all patients admitted to intensive care units (ICUs). Such wide variation can be explained by the

ample heterogeneity between different types of ICUs, that is, ICU for trauma patients or ICU for cardiac patients, for instance[8,11]. In most developed countries, the incidence of severe sepsis is between 50 and 100 cases per 100,000 people in the general population [8,12]. The incidence of sepsis is 3-4 times higher because of the relative percentage of patients who develop organ dysfunction and meet the criteria for more severe definitions (severe sepsis or septic shock) [8,13]. Studies have shown that sepsis is associated with annual estimates of 750,000 hospitalizations, 570,000 visits to emergency departments, 200,000 deaths, and US$ 16.7 billion in medical costs in the United States [13-16]. The incidence of sepsis is influenced by a number of patient-specific factors. Age is a well-known factor playing a key role in the increased risk for developing sepsis, as well as several other comorbid conditions. Perhaps the most widely known comorbid conditions are HIV infection, cancer, and diabetes, which can affect the immune system [17]. Respiratory infections usually are the most common cause of sepsis, severe sepsis, and septic shock [8,13,18,19]. Many recent epidemiological studies have shown that Gram-positive bacteria became the most common cause of sepsis in the past 25 years [8,13].

The incidence of sepsis, severe sepsis, and septic shock has been increasing. Advances in early detection and treatment have caused decreased mortality rates in patients with sepsis. However, because the incidence of sepsis has increased in recent years, the number of people who die each year continues to increase [8,20,21]. Therefore, efforts to establish early diagnosis and treatment of sepsis should continue to be encouraged.

Pathophysiology

SIRS is related to the changes in the body due to the course of the inflammatory process. Inflammation is triggered by responses to excessive stimulation of inflammatory mediators or injuries due to infectious or noninfectious processes [22-24]. Because it is a key component of the defense and cleaning mechanisms of the body, the inflammatory response releases chemical mediators that will guide the inflammatory process in order to maintain homeostasis within the body. These chemical mediators are recruited to guide the changes in the body related to the removal of harmful agents, such as microorganisms, endotoxins or other aggression processes. Such mediators are responsible for triggering the clinical and pathological manifestations of inflammation, sepsis, and shock [22-26]. The inflammatory response starts when a harmful agent is detected. Then, the inflammatory mediators that will act in small vessels are recruited. These mediators will trigger vasodilatation of arterioles, thus increasing blood-vessel capacity, and vascular permeability, as well as recruiting leukocytes [27,28].

Although these responses are aimed at providing benefits to the body, excessive pro-inflammatory response causes loss of homeostasis, an acute circulatory failure occurring together with metabolic alterations and chain reactions that may develop into a multiple organ dysfunction [26]. Vasodilation decreases venous return and cardiac output; therefore, tissue perfusion is also reduced. When there is persisting decreased cardiac output, there is also vasoconstriction of peripheral arterioles in an attempt to preserve normal blood pressure levels. Vasoconstriction and blood stasis, with progressive reduction of tissue perfusion, trigger the anaerobic metabolism, thus producing lactic acidosis, which causes vasodilation, further reducing the venous return. In addition, there is pulmonary hypertension, decreased right ventricle output, and decreased blood oxygenation [28].

Increased vascular permeability, which is caused by increased intercellular spacing between endothelial cell junctions, allows plasma proteins to leave the vessel, resulting in loss of fluids into the interstitium, thus causing edema and hypotension. Hypoproteinemia and hemoconcentration increase blood viscosity and blood stasis in peripheral capillaries, resulting in heat, redness, and pain [24].

Furthermore, circulating leukocytes, mainly neutrophils, cross the endothelium and migrate into injured tissues via chemotaxis. When leukocytes are activated, they can release proteolytic enzymes and toxic metabolites that will trigger tissue damage [24]. The damaged endothelium attracts greater number of leukocytes and platelets, which adhere to the wall of the vessel and occlude microvessels, thus reducing blood flow and increasing the imbalance between oxygen supply and demand, the demand increases because of the request of mediators [24].

Therefore, SIRS, which started with a peripheral vasodilation with increased vascular permeability, may reduce blood volume and be associate with the myocardial depressant factor (released by the ischemic pancreas), resulting in decreased tissue perfusion, hypoxia, ischemia, and death. Based on this context, understanding the pathophysiology and criteria of SIRS is essential to achieve early detection and treatment in an attempt to restore balance and prevent MODS.

Immunological and Coagulation Aspects in Sepsis

Sepsis and SIRS have the same clinical manifestations; however, in patients with sepsis, the inflammatory response is related to a suspected or documented infectious agent [5]. The presence of infection, and the subsequent development of sepsis, depends on a complex interaction between the defense mechanisms of the host and the virulence factors and escape mechanisms of the pathogens.

The first line of defense against infections is innate immune response. Even before the direct interaction between the immune cells and infectious agent, there are several barriers forming the innate immune defense. These barriers are anatomical (skin, a mechanical barrier; mucous membranes, with cilia and mucus production), physiological (body temperature; low pH in some sites; and chemical mediators, such as lysozyme, interferon, complement), phagocytic, and inflammatory [13].

Once pathogens meet innate immune cells, these cells recog-

nize the pathogens through pathogen-associated molecular patterns (PAMPs), specific molecules expressed by groups of pathogens. These molecules often determine the virulence and survival of the pathogenic agents. Because these molecules are shared by many pathogens, the recognition of PAMPs results in a wide but nonspecific defense action, that is, the response is fast, but limited. PAMPs are identified after binding to pattern recognition receptors (PRRs), which are expressed on the membrane of innate immune cells [29].

The most widely studied example of this interaction between PAMPs and PRRs are Toll-like receptors (TLRs), such as TLR-4, which is expressed by macrophages, dendritic cells, and neutrophils [22]. TLR-4 recognizes and binds to the lipopolysaccharides (LPS) of gram-negative bacteria, and it may be involved in the identification of viral proteins. Likewise, there is a Toll-like receptor (TLR-2) that identifies gram-positive bacteria. TLR-2 binds to the peptidoglycan of gram-positive bacteria [23]. Other members of the Toll family play a similar role in the innate immune response. TLR-3 is known to be involved in the identification of RNA double helix; TLR-5 recognizes flagellin; and TLR-9 differentiates unmethylated CpG sequences of bacterial DNA [24].

When TLRs bind to their respective patterns, there is activation of an intracellular signaling cascade causing the secretion and release of cytokines and leading to the development of inflammation and SIRS. Progression to severe sepsis and septic shock is strongly influenced by specific factors, such as polymorphisms in TLRs [25] and excessive or normal release of TNF-alpha and IL-1 [30].

The intracellular proteins NOD (nucleotide-binding oligomerization domain) and MyD88 (myeloid differentiation protein 88) participate in intracellular signaling after binding TLRs and PAMPs [26]. This interaction leads to the activation of NF-kB, a nuclear factor for gene activation and transcription of many cytokines related to SIRS, [27] such as 1 (IL-1), 2 (IL-2), 6 (IL-6), 8 (IL-8), 12 (IL-12), TNF-α (tumor necrosis factor alpha) and TNF-β (tumor necrosis factor beta) [19]. In addition to the pro-inflammatory cytokines mentioned above, patients with sepsis also produce anti-inflammatory cytokines related to tolerance, such as interleukins 4 (IL-4), 5 (IL-5), 10 (IL-10), 11 (IL-11), and 13 (IL-13) [31].

This simultaneous production of pro- and anti-inflammatory mediators is mainly regulated by monocytes/macrophages, [28] either by enabling more T helper 1 lymphocytes (which stimulates the synthesis of inflammatory cytokines and occurs if macrophages phagocytize bacteria or necrotic cells) or more T helper 2 lymphocytes (which induces tolerance if apoptotic cells are phagocytized) [30]. In patients with sepsis, any imbalance in these two conditions is related to mortality, either because of progression to severe sepsis and septic shock – influenced by TNF-alpha and IL-1 – or because of excessive induction of anti-inflammatory response. Such anergy leads to a state of immunosuppression and susceptibility to pathogens, which, in sepsis, may be called [28]. immunoparalysis, window of immunodeficiency, or compensatory anti-inflammatory response syndrome (CARS) [28].

The activation of the coagulation cascade is also an important factor found in sepsis and mainly in septic shock [32]. This system is activated by tissue factor expression and inhibition of endogenous anticoagulant factors – antithrombin III, protein C, protein S, and tissue factor pathway inhibitor (TFPI), which accelerate fibrinolysis [28]. In patients with sepsis and septic shock, in addition to the increased expression of tissue factor (which occurs due to endothelial damage mediated by pro-inflammatory cytokines, LPS, or even hypoxia), there are low levels of endogenous anticoagulants [30]. This may be due to the fact that LPS and TNF-α reduce the levels of thrombomodulin and endothelial protein C receptor (EPCR), [30] two mediators of protein C activation. Furthermore, LPS and TNF-α increase the levels of plasminogen activator inhibitor-1 (PAI-1), [30] which inhibits fibrinolysis.

Low levels of antithrombin are also related to sepsis. Mortality rates of 90-100% have been described in surgical patients with sepsis after trauma, whose levels of antithrombin were below 70% and 60%, respectively [33]. Low serum level of antithrombin is a predictor of infection and complicated prognosis in polytrauma patients [34]. In addition, antithrombin levels below 54% on the first day of severe sepsis is an independent predictor of death [35].

In patients with sepsis or septic shock, activation of the coagulation cascade is a reason for concern when it triggers the development of disseminated intravascular coagulation (DIC). This condition is characterized by activation of intravascular coagulation, fibrin formation and deposition in the microvessels, platelet consumption, and fibrinolysis changes [28]. After generating widespread blockage of the vascular flow to organs and tissues, this condition may lead to multiple organ dysfunction and increased risk of major bleeding (coagulopathy due to consumption of coagulation factors), thus being associated with high mortality rates.

Current Diagnosis and Neutrophil Cd64 in Sepsis

A large number of biological substances have been investigated as candidate biomarkers and/or mediators of sepsis. C-reactive protein (CRP), procalcitonin, interleukin-6 (IL-6), and interleukin 18 (IL-18) are considered useful in the diagnosis of sepsis and classification of sepsis severity; however, there are limitations [36-38]. More recently, attempts to demonstrate the clinical usefulness of these substances as biomarkers of sepsis have been documented for a wide variety of molecules, including high-mobility group protein B1 (HMGB1-) and triggering receptors expressed on myeloid cells (TREM1-). Some biomarkers of sepsis, such as cytokines, are also considered important mediators of sepsis, and the modulation of these substances plays a key therapeutic role [39]. Also, it is expected that the definition of a joint use of multiple molecular markers and/or more accurate prognostic scores of severity may allow predicting the outcome of sepsis [40].

Recent studies have focused on the investigation of neutrophil CD64 as a possible biomarker for the diagnosis of sepsis. This surface antigen is a receptor of the immunoglobulin fam-

ily usually expressed on monocytes and weakly expressed on non-activated mature neutrophils [41]. When neutrophil CD64 is strongly expressed on neutrophils, it means neutrophils were activated, thus suggesting the presence of bacterial infection or acute fungal infection [42]. Therefore, this antigen represents a physiological process that plays a key role in the innate immune response: neutrophils that act like phagocytes [43-46].

The expression of this antigen has been suggested to be a diagnostic marker for the evaluation of infection [47]. The CD64 index increases from five to ten times during the immune response to bacterial infection in preterm infants and children [48]. This suggests that neutrophil CD64 may be a useful tool for the early detection of infection [41,49]. It is believed that there is an increase in the CD64 expression levels in neutrophils in the beginning of sepsis [46].

Neutrophil CD64 has several characteristics that make it suitable for clinical use: its expression is low in resting neutrophils, whereas its expression increases significantly after activation. Once the stimulation factors are absent, neutrophil CD64 expression returns to baseline level within a few days [51]. In addition, neutrophil CD64 is relatively stable after blood sample collection; the test used for its detection is simple, requiring only a small blood sample.

Ng et al [45]. demonstrated sensitivity of 97% and specificity of 71% for the analysis of neutrophil CD64 in the early sepsis. Whereas Streimish et al. found sensitivity of 100% and specificity of 86% for the analysis of neutrophil CD64 in early neonatal sepsis [51,43,52].

Discussion

Neutrophil CD64 has been investigated in recent years as a biomarker because its characteristics suggest good clinical applicability to sepsis, which is a potentially serious disease and its progression dependents on early diagnosis and treatment.

In an attempt to find updated information on neutrophil CD64, we searched the PubMed database, which is the database of medical and biomedical international literature of the NLM (National Library of Medicine, USA) including references and abstracts of over 5,000 articles published in biomedical journals in the United States and 70 other countries. This database is updated once a month. Our search was conducted using the keywords “CD64” and “sepsis”, including articles published between 2009 and 2014. This search retrieved 43 articles. Of these, we selected 26 articles containing the keywords “CD64” and “sepsis” in the title. Of these, 20 articles were conducted with children and/or newborns and, therefore, were excluded from our study. Thus, six studies about neutrophil CD64 in adult patients with sepsis and published between 2009 and 2014 were included in our final analysis. Their main findings are described below.

Icardi et al. [36] examined the CD64 index with blood cultures from 109 patients for 2 months. Based on these analyses, these authors demonstrated sensitivity of 94.6% and specificity of 88.7% for blood cultures with bacterial growth related to CD64 index values above the cutoff point. The positive and negative predictive values were 89.8% and 94%, respectively. Therefore, the authors concluded that, in addition to being easily performed, the CD64 index is a useful and inexpensive test to improve the diagnosis and treatment of patients with bacterial infection.

Gámez-Diaz et al. [37] evaluated patients who arrived at the emergency department with diagnosis of suspected infection, fever, delirium, or acute hypotension analyzing clinical, microbiologic, laboratory, and radiologic data collected for each patient during the first 7 days of hospitalization.. They found sensitivity of 65.8% (95% CI = 61.1-70.3%) and specificity of 64.6% (95% CI = 57.8-70.8%) for neutrophil CD64 in sepsis.

Hoffmann [38] conducted a review of the literature on the implementation of neutrophil CD64 as a biomarker for sepsis. They analyzed eight studies, which corresponded to 907 patients. Based on these data, this author found high sensitivity and specificity in adults: 88.3% (95% CI 78.1-94.1%) and 87.6% (71.8-95.2%) respectively. This study also included ten publications (n = 1323) about the diagnostic performance of neutrophil CD64 in neonates, infants and children with sepsis. The sensibility found was 85.7% (95% CI = 77.5-91.2%) and specificity was 87.4% (95% CI = 79.3-92.6%).

Lewis et al. [39] evaluated the plasma of patients with sepsis to examine the CD64 expression and demonstrated increased CD64 levels in these patients. Most of the plasma samples from patients with sepsis increased the percentage of neutrophils CD64 (69% samples versus 17% normal plasma samples; $P < 0.001$). It is worth mentioning that such increase was only demonstrated in patients who developed sepsis. In patients with community-acquired infections who did not develop sepsis or in plasma from patients with acute or chronic inflammation who had no evidence of infection, an increased percentage of neutrophils CD64 were not seen. This effect reinforces the value of CD64 to diagnose sepsis.

Gerrits et al. [40] compared the CD64 index of patients with sepsis and SIRS admitted to an ICU with a control group of outpatients. They determined the CD64 index in residual EDTA blood samples from selected septic patients (n=25), SIRS patients (n=19), and OC patients (n=24). Beyond that, neutrophilic and eosinophilic granulocyte count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured simultaneously. The analysis identified higher CD64 levels in patients with sepsis when compared with SIRS and OC patients ($p<0.0001$). There was a statistically significant difference, with higher sensitivity and specificity than the other routine tests, such as PCR and leukocyte count.

Dimoula et al. [53] measured neutrophil CD64 expression at admission and daily until discharge or death. Blood C-reactive protein (CRP) level was also measured routinely. The authors found increased expression of CD64 in patients with sepsis, showing sensitivity of 89% (81%-94%) and specificity of 87% (83%-90%).When the results PCR and neutrophil

CD64 were combined, they found positive predictive value of 92% and negative predictive value of 99% for sepsis. There was also a decrease in CD64 values when the patients received appropriate antibiotics, whereas patients with inadequate antibiotic therapy continued to have high CD64 levels. Based on this analysis, the authors concluded that the combination of PCR and CD64 levels may be useful for the diagnosis of sepsis.

Conclusion

Sepsis is a potentially serious disorder requiring early diagnosis and treatment to prevent progression to multiple organ dysfunction. Several biomarkers have been investigated for the diagnosis and prognostic evaluation of sepsis. CD64 is a biomarker that has been studied within this context with promising results. Studies have shown good sensitivity and specificity for establishing early diagnosis of sepsis and evaluating the effectiveness of antibiotic therapy and prognosis. CD64 is also an easy-to-use and cost-effective biomarker.

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