Chapter 4

Biomarkers Utility for Sepsis Patients Management

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Abstract

Sepsis is a global problem in either developing or developed countries and it is expected that the number of patients with sepsis and septic shock will tremendously increase in next decades also because of the antibiotic resistance growing issue worldwide. Criteria for sepsis diagnosis and prognosis have been recently established, but still a further understanding of the role of biomarkers in this setting is needed. Better utilization of biomarkers such as white blood cell count, CRP, lactate, procalcitonin, presepsin and bioadrenomedullin in sepsis patients, a state of the art on how to use them is needed. This review will focus on the actual recognized role of sepsis biomarkers not only for diagnosis purpose but also to improve patients treatment results in order to reduce mortality, hospital length of stay and cost related.

Keywords: biomarkers, sepsis, patient management

1. Introduction

For about a century, sepsis has been defined as a systemic inflammatory response of the host to an infection. The lack of precise definitions and diagnostic criteria had also made difficult or even impossible to compare different studies and research. It was necessary to find a precise and standardized definition of sepsis, a common nomenclature to correctly diagnose the disease, allowing the creation of a targeted therapy for the patient [1]. The SIRS criteria were considered too sensitive and unspecific to be used in the identification of sepsis in most clinical practice [1, 2]. This scheme is based on four specific characteristics defined by the acronym PIRO:

- Predisposition, indicates pre-existing conditions potentially able to reduce septic patient survival;

- Insult or infection, reflects the pathogenicity of the microorganism;
- Response of the organism to the infectious event, including the manifestation of the SIRS;
- Organ dysfunction, which includes both organ failure and the failure of the coagulation system.

Sepsis

Documented or suspected infection.

Pathological process caused by the invasion of tissues, fluids or cavities of the host normally sterile by pathogenic or potentially pathogenic microorganisms, associated with some of the following signs and symptoms:

Variables:

1. Temperature > 38.3°C or < 36°C.
2. Heart rate > 90 min^{-1} or > 2 SD above the normal value for age.
3. Tachypnea.
4. Alteration of the state of consciousness.
5. Important edema or positive fluid balance (>20 mL/kg in 24 h).
6. Hyperglycaemia (>120 mg/dL) in the absence of diabetes.

- Inflammatory variables:

1. White blood cells >12,000 mL^{-1} or < 4000 mL^{-1}.
2. White blood cells in the standard but >10% of immature forms.
3. C-reactive protein>2 SD normal values.
4. Procalcitonin>2SD normal values.

- Hemodinamic variables:

1. Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg, or a reduction in SBP > 40 mmHg in adults or < 2 SD below normal for age).
2. SvO2 > 70%.
3. Cardiac Index>3.5 L min^{-1} m^2.

- Organ defunction variables:

1. Hypoxemia (PaO2/FiO2 < 300).
2. Acute oliguria (<0.5 mL/kg/h).
3. Increase of creatinine>0.5 mg/dL.
4. Abnormality of coagulation (INR > 1.5 or APTT>60 s).
5. Ileus (absence of peristalsis).
6. Platelet decrease (<100,000 mL^{-1}).
7. Hyperbilirubinemia (> 4 mg/dL).

- Tissue perfusion variables:

1. Hyperlactacidemia (> 1 mmol/L).

Severe sepsis

Sepsis associated with organ dysfunction (hypotension, hypoxemia, oliguria, metabolic acidosis and thrombocytopenia).

Septic shock

Severe sepsis with hypotension despite adequate fluid rehydration, along with the presence of organ perfusion abnormalities.

Table 1. SCCM/ESICM/ACCP/ATS/SIS – 2001 [3].

The use of this scheme is useful for defining, diagnosing and treating patients with sepsis but above all for obtaining better results in situations of severe sepsis and septic shock. The PIRO model is not yet fully defined and it has been debated [2]. **Table 1** summarizes the different definitions obtained after the two Consensus Conferences [3]:

Therefore, given the need to reexamine the current definitions, the "European Society of Intensive Care Medicine" and the "Society of Critical Care Medicine" have organized a task force of 19 specialists among infectiologists, surgeons, pulmonologists and anesthesiologists in order to review the data in the literature so far available.

Although SIRS criteria may be useful in the general diagnosis of an infection, they representative of an appropriate adaptive response of the organism, while sepsis involves an organ dysfunction that underlies a much more complex pathology; in this context the pro- and anti-inflammatory endogenous factors play a fundamental role and they are responsible for the inter-individual differences between patients [4–6].

The task force therefore suggests to use new values to decide to further investigate the search for organ dysfunction damage, to initiate or modify a therapy that is more appropriate and to consider patient's hospitalization in an Intensive Care [7]. **Table 2** reflects the conclusions reached by the task force and the implications in everyday practice, with the exemplification of the new diagnostic criteria and the new classification recognized by the International Classification of Diseases (ICD) [7].

Current guidelines and terminology	**Sepsis**	**Septic shock**
1991 and 2001 consensus terminology	Severe sepsis Sepsis-induced hypoperfusion	Septic shock
2015 definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis and vasopressor therapy needed to elevate MAP ≥65 mmHg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation
Recommended primary ICD codes		
ICD-9	995.92	785.52
ICD-10	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotic (oral or parenteral) in a specified period Within specified period around suspected infection: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mmHg and lactate >2 mmol/L (18 mg/dL)	

Table 2. Terminology and International Classification of Disease coding [7].

2. Sepsis in emergency department

Sepsis is a complex clinical syndrome that still represents a major challenge for today's medicine. In fact, despite the current possibilities of treatment, sepsis remains burdened by a high prevalence in the population and above all by a severe prognosis, representing one of the pathologies with the highest rate of morbidity and mortality. It is responsible for about one-third of all hospital admissions, and about 50% of ICU admissions. Mortality would reach 40%, of which 25% of deaths would occur within 48 h of entry into ICU [8].

In this complex scenario, the emergency doctor plays a key role. In fact, it depends on early diagnosis and treatment, the two factors that are recognized today as fundamental in the correct management of the septic patient as it is able to improve the prognosis. The enigmatic and often heterogeneous nature of sepsis, the absence of specific clinical and laboratory elements causes the lack of valid diagnostic tools, strongly influencing early intervention [9].

The recent literature has therefore placed great attention in the search for all clinical and laboratory factors, which can help in the rapid identification of sepsis and in the stratification of the risk of such patients, in order to make the treatment as aggressive as possible in terms of timeliness and effectiveness. More than two decades ago, sepsis was defined by the combination of an SIRS and an infection. This criterion, therefore useful for the correct diagnosis of sepsis, is also endowed with prognostic capacity, proving to be effective for the gravity stratification of patients with suspected infection due to the linking of these criteria with the presence of organ damage. However, the role of SIRS has been recently revised because although it has high prognostic power, it has little specificity being involved in a wide variety of pathologies regardless the presence of infection, in which the differential diagnosis often becomes difficult. Furthermore, it has been calculated that a certain number of patients with sepsis may not present SIRS criteria (about 1 in 8) [10]. The "Third International Consensus Definitions for Sepsis and Septic Shock" (Sepsis-3) [7] has therefore decided to go beyond the concept of SIRS, emphasizing rather the role of the organism's response to infection and organ damage (identified by a SOFA value ≥2) in the pathogenesis of sepsis.

3. Diagnosis

Sepsis diagnosis is established on the basis of patient's symptoms and clinical signs combined with radiological examinations and laboratory tests such as the search for biomarkers and identification of the microorganism responsible for the infection. In cases of sepsis, delay in diagnosis and antibiotic therapy affects the mortality of critically ill patients. Establishing diagnosis and therapy is very important but to hinder their definition it is difficult in differentiating sepsis from non-infectious stimuli in SIRS situations, symptoms and clinical signs, radiological and laboratory tests used for the diagnosis of sepsis are those reported in the previously reported tables, used in the definition of sepsis itself. The use of clinical scores, blood cultures and biomarkers for the diagnosis of sepsis will be discussed later.

4. Clinical scores

Since 2004, worldwide, the "Surviving Sepsis Campaign", consisting of a multidisciplinary team of specialists, periodically deals with the preparation and updating of documents on the general management of the septic patient and some specific aspects, such as timing and the optimal choice of antibiotic therapy, blood pressure support, glycemic control and oxygenation. In particular, at the last revision, the bundle of measures are implemented within the first hours after admission of the patient to reduce mortality was well defined [11].

At the same time, over the years, the need arose, especially in an intensivist environment, to identify those factors capable of predicting clinical severity and, in particular, the risk of death; for this purpose, many patient severity scores have been proposed and validated, useful from the moment of diagnosis to stratify the patient's clinical severity and, indirectly, to assess the risk of mortality [12].

The ideal prognostic score should have high sensitivity and high predictive value, be able to predict early mortality or clinical evolution, be rapidly usable, available everywhere, economic, objective and non-observer-dependent. Currently, no clinical score has all these characteristics. In particular, the two basic requirements of a prognostic system are the power of discrimination and calibration [13].

There are several works that have evaluated in the emergency medicine settings, the applicability of different gravity scores. In particular, simpler models to be calculated than those commonly used in Intensive Care Unit (ICU) have been proposed [11]. In 2003, Shapiro et al. have proposed the adoption of a new prognostic model, called Mortality in Emergency Department Sepsis (MEDS), as a method for stratifying patients afferent in emergency medicine with suspected sepsis [14]. Sankoff et al. resumed the MEDS score and carried out a multi-center prospective study to verify its reproducibility and validity [15]. The MEDS is the only score designed to be used in the septic patient in settings different from ICU. Numerous prognostic models born to be used in ICU were subsequently applied in different care settings, primarily in emergency medicine.

In one of the best known studies, Jones et al. have proposed the adoption of the Sequential Organ Failure Assessment (SOFA) score as a tool to predict the outcome of patients with severe sepsis with signs of hypoperfusion or septic shock. The authors considered all patients over the age of 18 with sepsis and evidence of hypoperfusion (systolic BP <90 mmHg or lactate levels>4 mmol/L); calculated the SOFA score at time zero and after 72 h (delta SOFA). The outcome of the study was to evaluate in-hospital mortality, the possible correlation between the difference in SOFA between admission and after 72 h, and finally mortality. The authors have shown a good correlation between the SOFA score at the entrance and the delta SOFA with the risk of in-hospital mortality. The limit of the work, similar to the studies on the MEDS score, is that it is an experience conducted only in a single center, which should be validated and extended to several centers to obtain a useful risk assessment tool [16, 17]. Alan E Jones et al. also demonstrated the usefulness of SOFA as a predictive prognosis score in patients with sepsis, and in particular in patients with severe sepsis with signs of hypoperfusion already on arrival in the emergency room [16].

The SOFA score (**Table 3**) is therefore a prognostic score, used for the prediction of mortality, based on the degree of dysfunction of six different systems and apparatuses, involved in the pathophysiology of the sepsis response. In particular, the respiratory, cardiovascular, renal, neurological, coagulative and hepatic systems are examined. The alteration of each of them indicates a condition of particular gravity, and the progression of the number of systems involved represents a negative prognostic variable. Thus, values < 9 predict mortality <33%, values between 9 and 11 a mortality of 40–50% and values>11 of 95%. Only one work assessed the accuracy of different prognostic models in septic patient assessment in a care setting of this kind [18]. The study, conducted in a single center, evaluated five different prognostic models MEDS, APACHE II, SAPS II, SOFA score (at time 0 and 24 h) and the Charlson index. The outcome examined was 28-day mortality, the number of patients examined was 140. The most accurate result was the 24-hour SOFA; however, also the SOFA at time 0, the maximum SOFA and increasing values of SOFA were related to mortality. It is useful to underline that the patients enrolled in the study already had a diagnosis of sepsis-septic shock with a mortality equal to 29%, much higher than the previously reported jobs (close to that of the IT departments). It is therefore reasonable to think that for a population of this kind, the use of a score

System	Score				
	0	1	2	3	4
Respiration					
PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3$/uL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12 (204)
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[b]	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (umol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FiO_2: fraction of inspired oxygen; MAP: mean arterial pressure; PaO_2: partial pressure of oxygen.

[a]Catecholamine doses are given as ug/kg/min for at least 1 h.

[b]Glasgow Coma Scale scores range from 3 to 15; higher score indicates better neurological function.

Table 3. Sequential (sepsis-related) organ failure assessment score [7].

validated in ICU (such as SOFA) may be more reliable than models validated in emergency medicine (such as MEDS) .

The shorter version of SOFA score, the qSOFA, evaluates only three clinical variables that are easily obtainable "bedside" which are systolic arterial pressure ≤ 100 mmHg, respiratory rate ≥ 22 times/min and alteration of the mental state (GCS ≤ 13 or other alteration). A ≥ 2 qSOFA would allow rapid detection of the septic patient and would be associated with 10% mortality. However, recent scientific studies have questioned the role of qSOFA, comparing it with the previous SIRS diagnostic criteria. In particular, a qSOFA ≥2 would seem to have high specificity but low sensitivity compared to a SIRS ≥2 value in the recognition of organ damage, and this could limit its use as a screening method [9].

5. Blood cultures

Blood culture is the "gold standard" exam to diagnose sepsis because it allows the etiological agent to be determined and provides the clinician with useful information for targeted therapy [11].

Several factors can influence the effectiveness and clinical significance of blood culture. In the pre-analytical phase, the withdrawal methods and the number of samples are very important. The sampling must be done when the first suspicions of infection arise and above all before the administration of any antibiotic, otherwise the therapy should be discontinued for a few hours or taken before the next administration of the antibiotic. In most episodes of bacteremia, it is necessary to collect two or three blood culture sets within 24 h to identify the pathogen, in case a single sample set is taken the probability of not identifying a patient with sepsis is about 35–40% [19].

An important factor for the accuracy of the diagnosis is the volume of blood present in the blood culture flask, in fact it is necessary to inoculate at least three colony forming units (CFU) per milliliter to get 100% positive; however, it is considered that in adult patients, in sepsis, the concentration per milliliter of blood is normally 0.1–1 CFU/mL, while in pediatric age the bacterial load is equal to 10–100 CFU/mL [20, 21].

Therefore, in the adult, the ideal amount of blood will therefore be 5–10 mL per vial and for pediatric patients of 1–5 mL. The ratio between the volume of the sample and that of the culture broth must allow the growth of many microorganisms, this ratio is 1:5–1:10 even if with the addition of substances that disable the inhibitory factors the optimal ratio is 1:5 [22–24]. Another important factor for a successful blood culture is incubation time.

The Clinical and Laboratory Standards Institute (CLSI) established that 5 days of incubation are sufficient to detect 95% growth of clinically significant bacteria (CLSI, 2007). Several studies have shown that in 97.5% of blood cultures containing a pathogen are positive after 3 days using automated systems [25, 26].

In the case of suspected endocarditis supported by demanding bacteria, or yeast septicemia or in pediatric patients, the incubation times are prolonged. Moreover, a possible administration of a therapy prior to sampling or the presence of a pathogen with particular nutritional needs lowers the ability of the investigation to identify the microorganism, in fact it has been shown that the levels of analytical sensitivity vary between 8 and 88% [27].

A limitation of blood culture is the lack of sensitivity in the search for particular bacteria that are often responsible for community-acquired pneumonia, such as *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae* and other germs that are difficult to grow or even non-cultivable such as *Coxiella burnetii*, *Francisella tularensis*, *Bartonella* spp., *Rickettsia* spp. and *Nocardia* spp. [28, 29].

The value of blood culture as a diagnostic test for bacteraemia and sepsis is limited, in fact, it emerges that in 50% of cases, the blood culture is negative even if the diagnosis of sepsis is certain and also the first results are provided after 48 h to conclude analysis with the identification and sensitivity to the pathogen's antibiotics after 5 days or more [1, 30, 31].

6. Sepsis biomarkers

6.1. Introduction

The current gold standard for the diagnosis of infections of the circulatory stream is blood culture, unfortunately its important limitation is the time necessary to complete the survey that goes from 1 to 5 or more days in the case of suspected sepsis caused by yeasts. The ideal situation would be to analyze the patient's on-site blood and provide all the necessary information to immediately target a targeted antibiotic therapy, and then the test should provide data for therapy evaluation by measuring the clearance of pathogenic nucleic acids in the blood in a certain period of time.

The ideal molecular test does not exist but these characteristics will have to be set as a long-term objective in the design of new molecular techniques for the diagnosis of sepsis.

A short-term objective is to analyze blood in parallel to culture methods and identify pathogens responsible for infection including non-cultivable organisms, and also to detect some of the determinants of drug resistance [30]. The molecular techniques currently available on the market can be distinguished in those based on the principle of amplification of the bacterial and/or fungal genome and those that exploit the principle of hybridization. Blood culture coupled with molecular investigations involves some disadvantages inherent to the traditional method such as delay in response with its possible alteration due to an unsuitable collection and the inability to provide the nutrients necessary for the development of demanding microorganisms. In the market, there are several kits in molecular biology that identify the pathogen from positive blood culture samples.

In the medical field, a circulating biochemical marker is defined as a demonstrable, therefore measurable, substance in the blood whose variation in concentration constitutes the signal of the presence of a pathology [32].

Regarding the role of biomarkers in the management of sepsis, over time various molecules were analyzed that, taken singly or combined in a panel, could be able to allow rapid diagnosis and prognosis, and that in the near future could also be able to guide the therapy itself to improve the clinical response and management of these patients [33]. Among the various biomarkers, some are used daily in clinical practice. Among these great importance has always been attributed to the role of lactates. They are considered useful by the guidelines because they have a prognostic value, being related to disease severity especially for values

≥ 2 mmol/L. However, according to other authors, the additive prognostic role of lactates to qSOFA would not be significant [34].

CRP and PCT are routinely used in patients with suspected first aid infection. CRP, released as an acute phase protein in inflammatory states, has a high specificity but low sensitivity and is therefore used for its negative predictive value. PCT, on the other hand, has been shown to have diagnostic and prognostic value in the management of sepsis. It is released in the course of bacterial infections, being therefore aids in the differential diagnosis, and is also included within the guidelines as a valid aid in guiding antibiotic therapy, representing a "mirror" of the therapeutic response to infection, and for its high prognostic power.

More recently, however, we have focused on the role of adrenomedullin (ADM). It is a peptide that several studies have shown to increase in septic patients [35]. The secretion mechanism depends to a large extent on stimulation by the lipopolysaccharide of bacteria, and its plasma levels derive mainly from secretion by endothelial cells [36]. ADM plays a fundamental role in hyperdynamic response during the early stages of sepsis and its main function is vasodilator [37]. After demonstrating the prognostic role of its precursor MR-proADM [38], thanks to a novel instrument based on a chemiluminescent sandwich detection (in which specific monoclonal antibodies are used against the C-terminal part of the peptide), today, it is possible directly measure the biologically active molecule (Bio-ADM or ADM). Thus, in a study published in 2014, our group showed that ADM values are significantly higher in patients with severe sepsis and septic shock than those with sepsis [39]; in particular, ADM, considered one of the most potent endogenous vasodilators, was found to be closely related to low mean arterial pressure (PAM) values and to the need to use vasopressors, thus detecting septic shock markers. Furthermore, higher values have been correlated with greater probability of death; and finally, the detection of multi-stroke ADM has proved to be fundamental in identifying patients with a worse prognosis [39].

From what has emerged, considering that sepsis determines endothelial dysregulation, excessive vasodilatation and consecutively collapse of arterial pressure and micro-vascular homeostasis and that ADM has as its main function vasodilator and therefore regulator of vascular tone, new studies currently in progress and still in the experimental phase, are directed to the development of a murine anti-ADM monoclonal antibody (HAM1101) that can become a therapy in septic shock, according to the hypothesis that it can improve the hemodynamics and perfusion of the organs and, consequently, also reduce the incidence of acute renal failure. To date, a humanized antibody has been selected, the HAM8101, which will be the subject of phase III experimental studies in the near future [39, 40].

Establishing diagnosis and therapy is very important but to hinder their definition is the difficulty in differentiating sepsis from non-infectious stimuli in SIRS situations, especially in those critically ill patients who may have developed SIRS for other causes such as pancreatitis, trauma, burns, etc. Therefore, the detection of an accurate biomarker in sepsis is decisive in critical situations with the ability to exclude or confirm an acute bacterial infection, to evaluate the systemic inflammatory response to infection and the host response to the established therapy [41].

An ideal biological marker must have different characteristics:

- useful in early diagnosis, provide information for a definitive diagnosis or help to identify a probable diagnosis;

- provide information regarding the prognosis including the patient in subpopulations whose outcome is better/worse than the population in question;
- provide, in the clinical course, useful information on how the patient responds to therapy and eventually help in modulating the therapeutic strategy;
- high specificity and sensitivity;
- have a clinically useful half-life time;
- be easily determinable and reproducible and difficult to influence by disturbing factors;
- have low costs and be easily used to quantify intervention actions, costs and benefits;
- in the case of sepsis, allow differential diagnosis between infectious and non-infectious etiology.

The use of biomarkers must always be integrated with the information deriving from a careful medical history collection, from a complete clinical objective examination, from the results of laboratory analyzes and diagnostic methods required in different cases. In fact, only the set of all these elements make it possible to reduce the number of evaluation errors deriving from a hasty decision, often dictated by superficiality or by incorrect knowledge. At present, there is no biomarker that ensures 100% correlation with a single pathology. In fact, we speak of "highly significant values" for a given pathological condition. Other potential uses of biomarkers include their prognostic role and, consequently, the ability to drive antibiotic therapy and to evaluate the response to the therapy itself, identifying those patients who most likely will face complications and organ dysfunction [32].

In the literature, there are many biomarkers already evaluated, such biomarkers for chemokine, cellular, receptor, hemostasis and vascular and others [42].

The available markers for the diagnosis of sepsis are numerous. There are leukocyte count, C-reactive protein (CRP), procalcitonin (PCT), endotoxin, cytokine, IL-1 receptor, complement factors, endothelin-1, ICAM-1 and VCAM-1, fosofolipase A2, PGE2, lactoferrin, neopterin, elastase, different interleukins (ILS), adrenomedullin (ADM) and proADM, atrial natriuretic peptide (ANP) and proANP, pro-vasopressin (copeptin), interferon-γ (IFN-γ), triggering receptor expressed on myeloid cells 1 (TREM-1) and resistin [41–44]. In several recently published studies, the most relevant biomarkers used, as they have a high diagnostic and prognostic capacity are CRP [45], PCT [46], ADM [47], copeptin [48], natriuretic peptide (MR-proANP) [49], presepsin (or CD 14 ligand) [50] and suPAR [51].

Unfortunately, in the sepsis, an ideal marker has not yet been identified and those normally used (fever, leukocytosis, CRP, PCT, etc.) often have little sensitivity and specificity, consequently they have limited use in patient management. Their dosage should be used and evaluated in the context of the clinical situation in which the patient is located and therefore it is essential to determine the appropriateness of the individual markers' request in collaboration with the clinician to exploit their potential to the full diagnostics, therapeutic monitoring and prognosis.

This section will discuss about white blood cell count (WBC), serum lactate, C-reactive protein (CRP), procalcitonin (PCT), presepsin and bioadrenomedullin as biomarker of sepsis.

6.2. White blood cell count (WBC)

White blood cell is a part of innate immune response by localizing infection. Otherwise in systemic sepsis process, there is profound leucocyte activation. Systemic sepsis also leading to organ damage and organ dysfunction attenuated by inhibition of leukocyte-endothelial interactions, systemic leukocyte activation and disseminated leukocyte adhesion [52].

The WBC results were considered abnormal if both the total number of neutrophils and the immature/total neutrophil ratio were abnormal simultaneously [53]. The sensitivity and specificity WBC for sepsis diagnosis in the literature vary widely, since there are significant differences in definitions used to count total neutrophils and sub-fractions; with sensitivity varying from 17 to 100% and specificity from 31 to 100%. A study by Caldas et al., reported that combination of WBC and CRP had sensitivity better than WBC alone [54].

In 2001, Zahorec introduced the use of neutrophil and lymphocyte count ratio (NLCR) as one of infection marker [55]. There is also correlation between NLCR and disease severity, also predictor for bacteremia [56].

The sepsis criteria recently changed from Sepsis-2 to Sepsis-3 highlighting on life-threatening organ damage caused by dysregulated host response to infection. This also affecting the use of biomarker in the diagnosis of sepsis, based on Ljungstrom et al., the AUC of NLCR to predict positive culture was 0.71, similar to previous study by Loonen showed AUC of 0.73 and 0.77 [56–58].

6.3. Serum lactate

Lactate is an important source of energy, particularly during starvation. Lactate also contributes to acidic environment by converting to lactic acid. Lactate value of 1400–1500 mmol/L per day resulted from anaerobic glycolysis activity as the reduction of pyruvate, moreover in tissue hypoxia [59]. Excretion of lactate mostly occurs in liver (60%) followed by kidney (30%) and other organs [60]. Shock status, such as cardiogenic or septic shock, is an important source of lactate production. The mortality rate was 46.1% for patients with both hypotension and lactate ≥4 mmol/L, 36.7% for septic patients with hypotension alone and 30% for patients with lactate ≥4 mmol/L alone [61, 62].

According to the new definition, septic shock can be diagnosed under two circumstances. The first one is persistent hypotension and the second one is increase of lactate serum level for more than 2 mmol/L, with additional note that lactate cut off were changed from 4 to 2 mmol/L. Therefore, increase of lactate serum level for more than 2 mmol/L can be recognized as a sign of septic shock. This condition greatly affects by hypotension and the use of vasopressor which caused further tissue hypoxia [62].

Ljungstrom et al. showed lactate correlate well with Sepsis-2 criteria in diagnosis of sepsis and septic shock, with specificity, accuracy and DOR were 97, 92 and 56.3%, respectively, by using cutoff 3.5 mmol/L. The downside of lactate is that even lactate level alone is widely used for diagnosis in early sepsis, the elevated level is not considered specific for sepsis diagnosis, hence it is proven to be more valuable in predicting mortality. The suggestion is to use combination of several biomarkers including lactate in diagnosing septic and septic shock [56].

6.4. C-reactive protein (CRP)

C-reactive protein (CRP) is synthesized by the liver after the action of various inflammation mediators such as IL-1, IL-6 and IL-8. This biomarker is produced 4–6 h after the phlogistic stimulus, and doubles its concentration in the circulation within 8 h and reaches its peak in 36–50 h [2, 63, 64].

CRP has both pro-inflammatory and anti-inflammatory characteristics, its half-life is 19 h and its levels in the blood stream remain elevated for a few days after the infection has disappeared [63]. Elevated plasma CRP levels indicate the presence of an infection and/or organ damage while protein synthesis will be significantly reduced in the case of hepatic failure [65]. The normal value of plasma CRP is <1 mg/dL, while it may increase up to 50 mg/dL in case of acute severe infection. The increase in CRP does not appear to be related to the severity of inflammation and also increases in cases of non-infectious diseases such as autoimmune diseases, acute coronary syndromes, rheumatic disorders, malignant tumors and after traumas or surgical interventions [66].

In conclusion, the values of CRP do not allow to distinguish between sepsis and SIRS of a non-infectious nature. This marker appears to be more sensitive than parameters such as the leukocyte count and the temperature but less specific than others such as PCT. However, CRP is a commonly used low cost and widely available marker.

6.5. Procalcitonin (PCT)

"Procalcitonin" (PCT) is a protein consisting of 116 amino acids, with a molecular weight of approximately 13 kDalton. The amino acid sequence of PCT is identical to that of calcitonin prohormone; it comprises the sequence of calcitonin from position 60 to 91 (32 amino acids). Through specific proteolysis, PCT (116 amino acids) and, in healthy intracellular individuals, calcitonin (32 amino acids) are released from this protein. Currently, four genes corresponding to calcitonin with homologies in the nucleotide sequence are known. These genes are all called "genetic family of calcitonin", although not all of them produce the calcitonin peptide hormone. The "CALC-I" gene, a candidate responsible for the production of procalcitonin induced by the inflammatory state, is one of the first examples of a process called "alternative splicing". The primary transcript can give rise to different mRNAs for inclusion or exclusion of the different exons present. Calcitonin encoding mRNA is the main product of CALC-I transcription in thyroid C cells, whereas CGRP-I mRNA (CGRP = calcitonin gene-related peptide) is produced in the nervous tissue of the central and peripheral nervous system (115). The plasma concentrations of procalcitonin in healthy individuals are very low, on the order of picograms, and in any case below the limits of determination of the test used for the immunoluminometric assay (<0.1 ng/mL, LUMItest PCT, BRAHMS Diagnostica, Berlin). PCT is a very stable protein in vivo and in vitro. In plasma it does not degrade to active calcitonin hormone; its in vivo half-life time is approximately 25–30 h [67] [115]. PCT production was stimulated in healthy volunteers through the intravenous injection of small amounts of bacterial endotoxin (lipopolysaccharide). PCT can be observed in the plasma 2 h after endotoxin

injection; between 6 and 8 h after the concentration of PCT increases rapidly up to a plateau about 12 h after injection. Over the next 2–3 days, the PCT values decrease until they reach their normal value [67, 68].

PCT concentrations above 0.5 ng/mL always indicate an acute infection or inflammation, with particularly high values in patients with severe bacterial infections in the acute phase and with septic inflammation. Plasma PCT concentration in the presence of serious infections and sepsis; however, can vary from 1 to 1000 ng/mL and PCT, in these cases, is probably not produced by C cells of the thyroid, but is inclined to believe that origin from neuroendocrine cells of the lung or intestine [67].

The release of PCT is determined only by the systemic reaction of the organism toward the infection, therefore local bacterial colonizations, encapsulated abscesses and localized and limited infections do not cause PCT release. In addition to bacterial infections, plasma PCT concentration has been shown to increase in acute forms of malaria and fungal infections. PCT, on the other hand, does not appear or appear to be not very significant, in the presence of viral infections, autoimmune diseases, neoplasia or traumatic surgery [69]. It could thus become one of the first-choice tests to be performed in patients with fever of unknown origin in the emergency room, to unmask an underlying bacterial infection [46, 70].

Bacterial endotoxins play the most important role in the mechanism of PCT release. At the end of the acute inflammatory reaction, the PCT concentration decreases according to the plasma half-life time. From these considerations it is clear that PCT, besides being a diagnostic marker of systemic bacterial infections, also has an important prognostic value. The medical literature, in fact, has shown the correlation between the severity of the clinical picture, the risk of development of multi-organ failure (MOF), long-term outcomes and one-year mortality, with plasma PCT values; in particular it was established that:

- high values of PCT protracted over time indicate an inflammation in progress;
- constantly increasing PCT levels are an unequivocal sign of poor prognosis;
- decreased PCT levels indicate favorable prognosis, improvement of inflammation or adequate therapeutic treatment of infection.

PCT thus becomes essential for the identification of patients at greatest risk, for guiding their therapy and for monitoring them over time [69, 71].

The areas in which the PCT could be used are numerous. In addition to patients who come to the emergency room with fever or suspected sepsis, PCT has been evaluated as both diagnostic [72, 73] and prognostic [74, 75] markers in pneumonia of bacterial origin. Even in this case, if associated with the clinical picture, the radiographic imaging and the values of the inflammatory indexes (CRP and white blood cells in particular), the PCT has shown to have a high predictive value as a biomarker. For the same reasons listed above, PCT should be measured in patients with significant dyspnea affected by COPD. The bacterial origin of exacerbations is often responsible for hospitalizations and mortality, and early intervention could reduce both of these two harmful consequences [76, 77].

Finally, an increase in PCT has also been shown in bacterial endocarditis [78] and in acute coronary syndromes [79, 80], while its prognostic use as a marker of infection has been exploited in the monitoring of patients undergoing major surgery [81].

Despite the wide space that scientific research has devoted to PCT, its exact mechanism of action still remains partially unknown. The rapid induction of PCT after administration of bacterial endotoxins and its relationship to cytokines, such as TNF-α, suggest the existence of a close correlation between PCT and pro-inflammatory cytokines, which earned him the name "ormokina" [82]. In the clinic, it was observed that there is a correlation between the timing of PCT, IL-6 and TNF-α. In acute inflammation, PCT values increase a few hours after the increase of IL-6 and TNF-α; at the end of the inflammation, the PCT begins to decrease after the decrease of the IL-6 and in any case before the CRP values start to decrease. This would demonstrate a pathophysiological function of PCT in the immune response. It would be responsible for increasing nitric oxide synthesis and monocyte migration to the site of infection [83].

6.6. Presepsin

Presepsin is another name for the sCD14 subtype (sCD14-ST), is a new biomarker associated with sepsis. Soluble CD14 subtype is one fragment of CD14 soluble that is a molecular fragment produced by plasma protease activity during the inflammatory process [84]. Presepsin is present in the cell membranes of macrophages, monocytes and granulocyte cells and said to play a role for the intracellular transduction of endotoxin signals [85]. Presepsin has close relation with infection and is found to increase significantly in sepsis.

Behnes et al. showed that presepsin was moderately significant to determine between sepsis and non sepsis patient, with slightly overlapping value of 817.9 ± 572.7 and 294.2 ± 121.4 pg/mL for sepsis and non sepsis patient, respectively [50]. The level of presepsin in serum usually raised within 2 h after infection and reach maximum level within 3 h, therefore it is useful in diagnosis of sepsis patient during early stages [86, 87].

Wu et al. reported a meta-analysis about diagnostic value of presepsin of some studies. The result showed that the sensitivity of presepsin ranged from 0.67 to 1.0, while the specificity of presepsin ranged from 0.33 to 0.98. The pooled sensitivity and specificity obtained by the HSROC method were 0.84 (95% CI 0.80–0.87) and 0.76 (95% CI 0.67–0.84), respectively. While ROC for presepsin showed the AUC was 0.88 (95% CI 0.85–0.90 [88].

When compared to PCT, presepsin showed similar diagnostic accuracy for sepsis with sensitivity 0.78 [95% CI: 0.76–0.80] and 0.77 [95% CI: 0.72–0.81], specificity 0.83 [95% CI: 0.80–0.85] and 0.79 [95% CI: 0.74–0.84], AUCs 0.89 [95% CI: 0.84–0.94] and 0.85 [95% CI: 0.81–0.88], for presepsin and procalcitonin, respectively, to diagnose patient with sepsis and SIRS without infection [89].

However, there are some superiority of presepsin over PCT. Presepsin raised earlier in the event of infection therefore can be used in earlier and faster in sepsis. The PATHFAST analysis system also allow presepsin assay on takes 17 min to be done, therefore can be used accordingly with the guidelines of diagnosis and treatment of sepsis.

6.7. Bioadrenomedullin

Adrenomedullin (ADM) is a peptide with 52 amino acids initially isolated from the adrenal gland. It is produced in many organs and tissues including the vasculature. ADM has numerous actions, including vasodilation, natriuresis, antiapoptosis and stimulation of NO production. ADM is released from the vascular wall and acts as an autocrine or a paracrine hormone to regulate vascular tone and blood pressure. It may also be involved in the different stages of the cardiovascular continuum as well as in the hemodynamic changes in septic shock [90, 91].

A study by Crain et al. showed that in critically ill patients on admission, there was a stepwise increase in MR-proADM levels from patients without infection (e.g. SIRS) to patients with sepsis, severe sepsis and septic shock. Median proADM levels was 1.1 nmol/L (0.3–3.7 nmol/L) in patients with SIRS, 1.8 nmol/L (0.4–5.8 nmol/L) in patients with sepsis, 2.3 nmol/L (1.0–17.6 nmol/L) in patients with severe sepsis and in patients with septic shock it was 4.5 nmol/L (0.9–21 nmol/L). There are two primary mechanisms that might be responsible for the marked increase in circulating MR-proADM and mature ADM levels in sepsis. The first mechanism, as a member of the CALC gene family, ADM is widely expressed and extensively synthesized during sepsis, just like other calcitonin peptides including PCT, that upregulated by bacterial endotoxins and pro-inflammatory cytokines [92]. The second potential mechanism is the decreased clearance of MR-proADM by the kidneys in sepsis that may be responsible for its increased level. This hypothesis is also supported by a significant correlation between MR-proADM and creatinine levels ($r = 0.76$; $P < 0.001$). The study showed increase of plasma ADM five times higher that normal individuals, that did not changed after hemodialysis. An ideal sepsis marker should permit early diagnosis, should inform about the course of disease, and should help one to differentiate bacterial from non-infectious and viral causes of systemic inflammation [90].

Recently, the combined use of two biomarkers, procalcitonin (PCT) and mid-regional pro-adrenomedullin (MR-proADM) has been reported in sepsis diagnosis and prognosis. In the last years, many articles have been published on the role of PCT and MR-proADM in the diagnosis and prognosis of bacterial infections in different settings. Angeletti et al. showed that MR-proADM differentiates sepsis from non-infectious systemic inflammatory response syndrome with high specificity and that the simultaneous measurement of MR-proADM and PCT in septic patients increases the post-test diagnostic probability compared to the independent determination of individual markers. A score derived from the combination of PCT and MR-proADM has been recently proposed as a useful clinical tool to provide rapid diagnosis as well as to suggest prognosis of bacterial infections. The combined score, calculated on the basis of defined score assigned for each PCT and MR-proADM value, can predict bacterial infections and differentiate localized infections from systemic infections, as suggested by receiver operating characteristic curve analysis. On the basis of the score values, localized infections could be differentiated from systemic infections and the severity of the infectious disease can be predicted. The importance of the use of this multi-marker approach in the diagnosis and prognosis of sepsis is more evident since the publication of the new definition of sepsis that has been updated assigned an important role to the organ dysfunction [93].

6.8. Comparison between biomarker of sepsis

Lactate should be evaluated at least within 24 h after emergency admission, the decrease of lactate after 24 h related to poor prognosis of the patients [94]. CRP can increase within 24–48 h duration to 1000 folds during the acute phase and decrease to low normal value after the acute phase [95]. Procalcitonin start to rise 3–6 h after infection occur and reach its peak on 6–8 h, then remained in the blood until 12–48 h [96]. Meanwhile presepsin increase faster within 2–3 h after sepsis developed and rapidly decreased after symptoms resolved [97] so it can be used to determine whether the treatment is successful in patient with sepsis.

Several conditions can increase lactate in any person, such condition as inadequate oxygen delivery oxygen demands mismatch and inadequate oxygen utilization [94]. CRP increase in bacterial infection as part of innate immune response [95, 98]. It can also increase in condition of inflammation even can predict the cardiovascular event such as the sign of atherogenesis and pathogenesis of myocardial injury and used as predictor in healthy individuals [99, 100]. It also can be a predictor of mortality in hemodialysis patient [101, 102]. Procalcitonin will rise in the event of sepsis, systemic infection and severe inflammation. Procalcitonin will not rise in the event of viral infection, autoimmune and neoplasma, but it can rise in some people with some neuroendocrine tumor such as medullare carcinoma of thyroid, small cell lung carcinoma and renal failure [96, 103]. Procalcitonin is also known to rise in person with trauma [97]. Some inflammation can trigger the rise of procalcitonin are pancreatitis [104], appendicitis [105], burns [106], heat stroke [107], multitrauma [108] and extensive surgery [109]. Presepsin do not increase in patient with trauma without associated infection, thus make it specific in patient with sepsis [97]. Presepsin also reliable in patient with sepsis and both acute kidney injury and those who do not, but it has caveats in patient with advanced kidney injury and end stage renal disease [110].

Head to head study by cochrane comparing procalcitonin, presepsin and CRP is still ongoing [111]. Several data about sensitivity and specificity of these parameters are already covered by some journal. The study about diagnostic value of lactate in cancer patient with sepsis showed for the cutoff value of lactate more than 1 mmol/L could predict sepsis with sensitivity of 86.36% and specificity of 28.12%, with additional data that the value were not different in patient with and without cancer [112]. Another study showed 34.0% sensitivity and 82.0% specificity at the cutoff point of 2.0 mmol/L that emphasized the low sensitivity but high specificity in diagnosing sepsis [113]. While other study measures prognostic value of lactate showed that lactate value over 4.0 mmol/L have increased mortality with sensitivity and specificity of 36 and 92%, respectively [114]. CRP found to be useful as part of screening in sepsis patient with sensitivity and specificity 98.5 and 75%, respectively, for cutoff value 5 mg/dL or more [115]. Another study use CRP as parameter for successful treatment in ICU patient showed that decreasing level of CRP by 25% or more are good indicator with sensitivity of 97% and specificity of 95% [116]. A study showed that sensitivity and specificity of procalcitonin were 75 and 79%, respectively [117]. While another study in patient with renal impairment proposed different cutoff to determine if patient is in septic condition, due to the caveats of procalcitonin in renal failure patient [118]. Another study comparing CRP, procalcitonin and presepsin showed advantage of presepsin, with AUC of presepsin was 0.845, compared to PCT (0.652), and CRP (0.815). With sensitivity and specificity of presepsin with cutoff value 600 pg./mL was 87.8 and 81.4%, respectively [84].

Availability and cost of these examination will be favored more on white blood cell count because it is part of routine practice everywhere, while for lactate, the difference between patient examined for lactate around $39.53/patient whereas the usual care cost $33.20/patient but the effectiveness in term of patient outcome and survival are better in those with lactate examination [119]. On the other hand, the use of CRP in England shows the use of CRP can also increase quality of treatment and decrease cost for patient which leads to fewer antibiotic prescriptions [120]. One study about procalcitonin use as part of management of patient with pneumonia find that procalcitonin although promising not significantly reduce cost of care, due to lack of data, since non adherence of the physician. This condition might be due to lack of experience of using procalcitonin and need for more guided protocol of procalcitonin use in patient [121].

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