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Review Article

Sepsis biomarkers: current information and future visions

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ABSTRACT

Sepsis is a complex inflammatory response that is strongly associated with multiple organ dysfunctions and considered as a major cause of morbidity and mortality worldwide. The early recognition of the causative agents of sepsis events is crucial and must be include accuracy when planning about standard and rapid laboratory procedures. To reduce the risk of death, prior studies relied on a variety of strategies, including cultural, immunological, and molecular methods for the early and precise management of sepsis. However, the mortality rate of sepsis is still high and there are not any predictive biomarkers for sepsis that may be used in clinical settings. The current study was interested in explaining the major role of some common parameters that were followed in clinical settings to improve the diagnosis of infectious agents before the cases of illnesses become complicated. The gold standard blood culture along with complete blood count (CBC), lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT), presepsin (PSN), pentraxin3 (PTX3), and monocyte chemoattractant protein-1(MCP-1) could detect the microbial bloodstream infection.

Introduction

Sepsis is an extremely complicated disease characterized by an abnormal immune response to infection, which results in an uncontrolled inflammatory response followed by immunosuppression. It develops as a consequence of infections acquiredin the community and in the hospitals, particularly in intensive care units [1]. In general, sepsis is an abnormal systemic disorder that displays a pattern of immune system response to infection,and it has become a global health concern

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[2].Hence, the rapid identification of causative agents is critical to prevent host damage and lowering the risk of death. Even though the detection of sepsis remains difficult due to non-specific signs and symptoms, numerous attempts have been made to identify an accurate biomarker for screening individuals at high risk of sepsis [3, 4, 5].Sepsis biomarkers, includingacute phase proteins such as CRP and PTX3,enzymes such as LDH, cells such asgranulocytesand lymphocytes, proteins such as PCT and PSN, as well as pro-inflammatory cytokines and chemoattractant factors such as MCP-1,may allow for early detection and management of sepsisby immediately initiation the treatment before the occurrence of adverse consequences. To utilize some sepsis biomarkers as indicators for detection of sepsis episodes, we must first understand what happens during the infection and how certain pathogens might go from pro-inflammatory to instigate hyper-inflammatory immune responses, eventually leading to severe sepsis. The host immune system responds to particular products from different pathogens. The outer membrane LPS of gram-negative bacteria, for example, represents a pathogen-associated molecular pattern (PAMP). Different forms of PAMPs are recognized by innate immune cells which cell surface receptors for them have known as pattern recognition receptors (PRRs) such as TLRs [6].

After the engagement between bacterial ligands (PAMPs) and their host cell surface receptors (TLRs) occurs, the innate immune cells such as macrophages become activated and generate pro-inflammatory cytokines including TNFα, IL-1β, and IL-6 cytokines. In the case of over production of these cytokines in response to some pathogens, they produce a condition that can be termed " early sepsis ", which takes place if the innate immunity fails to eliminate the pathogen.

For the initial assessment of sepsis, in 1991, an international consensus conference described sepsis as an infection that is combined with the characteristics of systemic inflammatory response syndrome (SIRS) such as changes in normal body temperature and abnormal (WBC) count [7]. Since the criteria for sepsis description are continually updated over time, in 2001, the experts changed the first description of sepsis to include other signs and symptoms. As a result, this update is therefore based upon the fact that the early definition of sepsis involves signs and symptoms that are insufficient to identify the infection in individuals [8].

Ten years later, Dr. Roger C. Bone helped to emphasize the relevance of a compensatory anti-inflammatory response syndrome (CARS), which commonly occurs after SIRS, particularly in individuals with severe sepsis [9]. This means that the pathogenesis of sepsis is progressive across the course of infection, and each stage has its own biomarkers. As a result, different biomarkers must be used to detect and monitor the course of sepsis. The pro-inflammatory cytokines generated by innate immune cells and CRP were considered as a potential indicator for sepsis before the discovery of the relationships between elevated levels of procalcitonin (PCT) and bacterial infection in the 1990s [10]. Hence, another indicator has been identified. An increase in the level of CRP and PCT were added to the modified criteria of sepsis in 2003. Recently, it has become much easier to distinguish the early and less severe from the late and more severe sepsis, as shown in **figure (1)**which summarized the development of sepsis manifestations during the infection.

The purpose of this research is tosummarize the potential role of some sepsis biomarkers in early detection the type of infection and identified their relatedness to the development of signs and symptoms in septic patients.

1. Parameters used in rapid screening tests

To avoid serious consequences and lower mortality, the quick identification of sepsis is essential. Therefore, the useful of rapid screening test offers a preliminary indication of the presence of a condition that may cause sepsis and is regarded as one of the key indicators for the early detection of sepsis.

1.1 Complete blood count (CBC)

A complete blood count is a common screening test for certain illnesses, and it is a significant tool because patients will usually have their blood count assessedwhen they present at the hospital [11].CBC was performed to detect white blood cells (WBC), granulocytes (GRA), lymphocytes (LYM),hemoglobin (HGB),hematocrit (HCT), red cell distribution width (RDW), andplatelets (PLT).Among all the sepsis indicators being studied, CBC values may be the most helpful because they can be easily performed, cheap, and are available in all medical facilities. This test is important for the early diagnosis of many health

issues, which should then be further investigated through laboratory examination [12].

The abnormal WBC value indicates the presence of acute inflammation caused by unidentified causative agents.The relative value is useful for determining which WBC population is primarily involved in the inflammatory process, providing anetiological diagnosis,where lymphocytes and granulocytes respond to microbial infection andthis responsiveness is characterized by the increase of granulocytes and decrease of lymphocytes count,or vice versa.Sepsis stimulates lymphocyte apoptosis, whichresults in lymphocytopenia [11].

Regarding RBC, Effenberger & Hartmann observed that sepsis is characterized by a decreased RBC count, which may be brought on by a number of mechanisms connected to the altered generation or survival of RBC [13] However, a lower RBC count has no diagnostic value for sepsis. Most patients develop anemia by day 8 throughout their hospitalization in an intensive care unit. [14].Hematocrit (HCT) is the percentage of RBC in a whole blood sample. A decrease in HCT percentage is a hallmark of sepsis [15, 16].The values of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) do not have a role in patients with sepsis. Furthermore, because RBC survival was reduced and maturation was suppressed during sepsis, the red cell distribution width (RDW) increased [17]. However, several researchers were unable to find a relationship between sepsis consequence and RDW [18].

Platelets (PLT) are one of the blood components. A comprehensive intravascular immune defense response is orchestrated by PLT to prevent the spread of bacteria by acting as sentinels for the quick detection of microbial invasion [19]. During sepsis, multiple processes, including the activation of the coagulation system, cause the activation of platelets. The surface of activated platelets expresses many receptors that either directly bind to and sequester external pathogens or stimulate the aggregation of neighboring platelets and leukocytes [20].A typical sign in septic patients is thrombocytopenia, or a decrease in platelet count. In fact, numerous writers have demonstrated that platelet count is an effective sepsis diagnostic and prognostic indicator [21].

The presence of acute inflammation caused by unidentified causative agents was indicated by an increase or decrease in normal value of CBC parameters. Since there is no single sepsis parameter that is perfect enough to detect sepsis, the CBC value with blood culture and other indicative biomarkers can provide essential clinical data to identify and treat sepsis.

1.2 Lactate dehydrogenase (LDH)

The LDH enzyme is present in all body tissues and allows the tissues to survive in a low-oxygen environment (hypoxic environment) due to its ability to anaerobically convert pyruvate to lactate during glucose metabolism [22]. It is another potent parameter for sepsis detection. Septic patients can be detected from the measurement the serum levels of LDH and heart beatings rate [23]. In cases of sepsis, elevated levels of lactate are typically indicative to decrease oxygen supply to the body cells (hypoxia) or reduced tissue perfusion, which results in anaerobic glycolysis [24].Although LDH is unreliable for determining the etiological agent of infection, it has an important role in identifying the severity of sepsis and monitoring the state of patients who reside in intensive care units.

1.3 C-reactive protein (CRP)

It is a well-known acute phase protein originating from the liver and has a normal serum level ranging from 0.8 mg/L to 3 mg/L in healthy individuals. CRP test is one of the most commonly used diagnostic tests to determine whether patients with sepsis have elevated levels in response to infection and inflammation. Once an infection has occurred, activated macrophages produce IL-6, that in turn stimulates the liver’s synthesis of acute phase proteins, such as CRP, and triggers more production of PMNs in the bone marrow [25].

Infections may be viral, bacterial, or fungal in nature. The infection could be either primary or secondary. Controlling infection and response to treatment in a patient is a big challenge,like treating infection in an immune-compromised or elderly patient.Here, sepsis biomarkers such as CRP have a crucial role from the time of the patient's presentation to the hospital until the final patient's consequence according to rising or decreasing CRP concentration of the patient [26].

Although the role of CRP during acute inflammation is unclear, it may adhere to the phospholipid components of bacteria, allowing macrophages to more easily remove them. The

serum levels of CRP rise considerably during acute inflammation; hence the test is used to detect the presence of infectious disease, particularly in children [27] and, used as a marker for the inflammation that associated with atherosclerosis and heart disease [28]. Even though it has low specificity as a biomarker of sepsis, it is often used to screen for early onset sepsis because its sensitivity is generally thought to be very high in this situation. C-reactive protein is also commonly used to follow patients after surgery; levels are normally elevated, but they quickly diminish unless a post-operative infection develops [29].

Finally, despite its relatively non-specific nature, the CRP is considered the first screening test because it provides evidence of specific infection caused by any microorganism, allowing other confirmatory tests to be performed later.

2. Parameters used as diagnostic tests

The pathogenesis of sepsis is progressive across the course of infection, and each stage has its own biomarkers. Hence, the ability to diagnose sepsis from CBC, LBH and CRP is limited. For further progressive in this investigations, different biomarkers must be used to detect and monitor the course of sepsis [9].

2.1 Procalcitonin (PCT)

Procalcitonin, a protein of 116 amino acids with a molecular weight of 13 kDa, was first discovered 25 years ago as an intracellular precursor of calcitonin. After being cleaved by endopeptidase (proteolytic enzyme), PCT transforms into active calcitonin, which plays a vital function in regulation of calcium concentration. Procalcitonin was recognized for the first time in the 1970s. It is formed in the thyroid gland by parafollicular cells (C-cells), and it is also generated by different cells throughout the body, such as neuroendocrine cells in the lung and intestine [30]. The normal value of thePCT in the blood stream is less than 0.1 ng/mL, whereas it rises within 2 to 4 hours during infection and has a half-life of 22 to 35 hours [31].

However, it is considered a sepsis biomarker because its higher value is associated with the bacterial infection [32]. PCT levels rise during the course of infection and inflammation in response to bacterial toxins and cytokines induced by immune cells in response to specific bacteria, such as IL-1, IL-6, and TNF. If the causative agent is effectively managed by the immune system and appropriate antibiotics, these high levels of PCT will decrease.It is not substantially increased during viral disease. This is because one of the host cell responses to a viral infection is the production of interferon (IFNγ) which impedes the initial creation of PCT [33]. Because of this preferential cellular mechanism, PCT is a valuable diagnostic marker that is more specific for bacterial infections than other inflammatory markers, and it also helps to distinguish between viral and bacterial infections.The importance of this protein in the diagnosis and monitoring the patients suffers from invasive bacterial infection, was discovered in the 1990s [34].Following research, it was discovered that PCT is a component of the systemic response that leads to severe sepsis. PCT, like CRP, may have pro-inflammatory properties. PCT has been recommended as a beneficial test for severely ill patients who develop a new fever [35].

However, the usefulness of PCT as a sepsis biomarker in recent years may have lessened the significance of CRP. In fact, several studies have been conducted in recent years to evaluate the diagnostic utility of PCT, usually in comparison to CRP. Recently, PCT value was found to be more efficient and more specific than other inflammatory biomarkers in cases of bacterial infection. Several clinical studieshave shown that it may be useful in predicting blood culture findings in patients who are suffering from severe sepsis [36]. Furthermore, PCT aids in the early identification of sepsis and differentiates between cases with symptoms of non-infectious SIRS and cases related to severe bacterial infections [37]. Moreover, PCT is not just separate test and should not be used in place of other important tests and clinical examination assessments of patients. PCT offers additional information and assists clinicians in making reasonable medical decision in patient cases. The usefulness of one biomarker to accurately predict of infection may be misleading. Despite the facts that it refers to the significant of the PCT levels for primary detection of sepsis, keep in mind that more than one marker must be used to achieve accepted results for such infection.

2.2Presepsin (PSN)

Presepsin is a plasma soluble form of CD14 (sCD14), which is cleaved from the main membrane-bound form of CD14 (mCD14). mCD14 is a member of pattern recognition receptors (PRRs), which is upregulated on the surface of the phagocytes as a receptor for various groups of

ligands particularly bacterial LPS endotoxin [38]. Presepsin was discovered as a novel indicator whose value was used in the diagnosis and management of sepsis [39].

As was earlier mentioned regarding the existence of non-infectious SIRS in many critical illness cases, the discrimination between SIRS and sepsis at the early stage of disease leads to an accurate diagnosis and accelerates treatment. Hence, in addition to CRP and PCT being recognized in various studies several years ago, presepsin was developed later to complement them in terms of sepsis diagnosis and assessment. Presepsin in the blood circulation indicates that phagocytes have been activated in response to infection [40]. The reference value of presepsin ranges from 55 to 184 pg/ml [41]. As with PCT, PSN has a powerful diagnostic accuracy, according to a recently published meta-analysis comparing PSN with other biomarkers. In addition to that, presepsin is also used for early detection of a probable bacterial infection and to predict the risk of death due to its level gradually increasing with the progression of sepsis events [42].

Despite the fact that it has received a lot of attention from investigators, the clinical relevance of presepsin has remained ambiguous or controversial till now. However, in severalstudiesthe serum levels of presepsin were assessedand it was found that it can be a more reliable biomarker for the diagnosis of bacterial sepsis.

2.3 Pentraxin 3 (PTX3)

The ambiguity of the sepsis events and their causative agents led that the researchers to exert more effort to find new biomarkers that could help to improve the diagnostic methodologies. They also hypothesized that using multiple biomarkers would increase the diagnostic value compared to using a single biomarker because sepsis is formed up of a range of signaling proteins from diverse cascades.

Pentraxin 3 is another new protein that acts as a significant mediator of the innate immune system against different types of pathogens and has a potent role in complement component activation [43]. PTX3 is also employed as a diagnostic marker for bacterial-originated sepsis. PTX3 is an acute phase protein and represents the soluble form of pattern recognition molecules that is structurally like CRP but is produced by different innate immune cells including dendritic cells, neutrophils, fibroblast, epithelial, and endothelial cells rather than the liver [44]. PTX3 has a normal value of less than 2 ng/ml in healthy individuals, but it can be promptly increased in cases of inflammation when inflammatory cells generate and release it in response to pro-inflammatory cytokines including IL-1β and TNFα [45].

PTX3 has an essential role during the acute phase of inflammation because it binds to C1q protein and activates the classical pathway of the complement component system to facilitate pathogen recognition by phagocytic cells such as macrophages and dendritic cells. Hence, its function as an opsonizing protein, facilitating pathogen identification and engulf it [46]. Furthermore, there is evidence referring to the interaction between PTX3 and tissue factors expression, which induces coagulation stimulation during sepsis [47].

The study of PTX3 in sepsis could lead to a better understanding of the pathogenesis of this condition and, potentially, the development of more effective treatments. Further research is needed to prove the specificity of PTX3 in the diagnosis of sepsis.

2.4Monocyte Chemoattractant Protein-1 (MCP-1)

Chemokines are chemotactic cytokines that constitute a large family of chemoattractant proteins and are grouped into four families according to the spacing and arrangement of the first two cysteine residues in their N-terminus, which are CX3X, CXC, CC, and C. Based on their behaviors, the main roles of these signaling proteins are to recruit leukocytes and other cells to the site of infection, leading to activation of the innate immune system [48]. Chemokines play a crucial role in immune response [49, 50]. Monocyte chemoattractant protein-1 is a member of the CC family (CCL2), with a normal serum level of 69.5 up to 175.2 pg/ml in healthy individuals [51]. MCP-1/CCL2 is encoded by genes located on chromosome 17 and secreted in response to pro-inflammatory cytokines to regulate the migration and infiltration of the innate immune cells particularly mononuclear cell during injury or infection.CCL2 and its receptor, CCR2, have been shown to be induced and involved in a wide range of illnesses. Several studies attempted to use MCP-

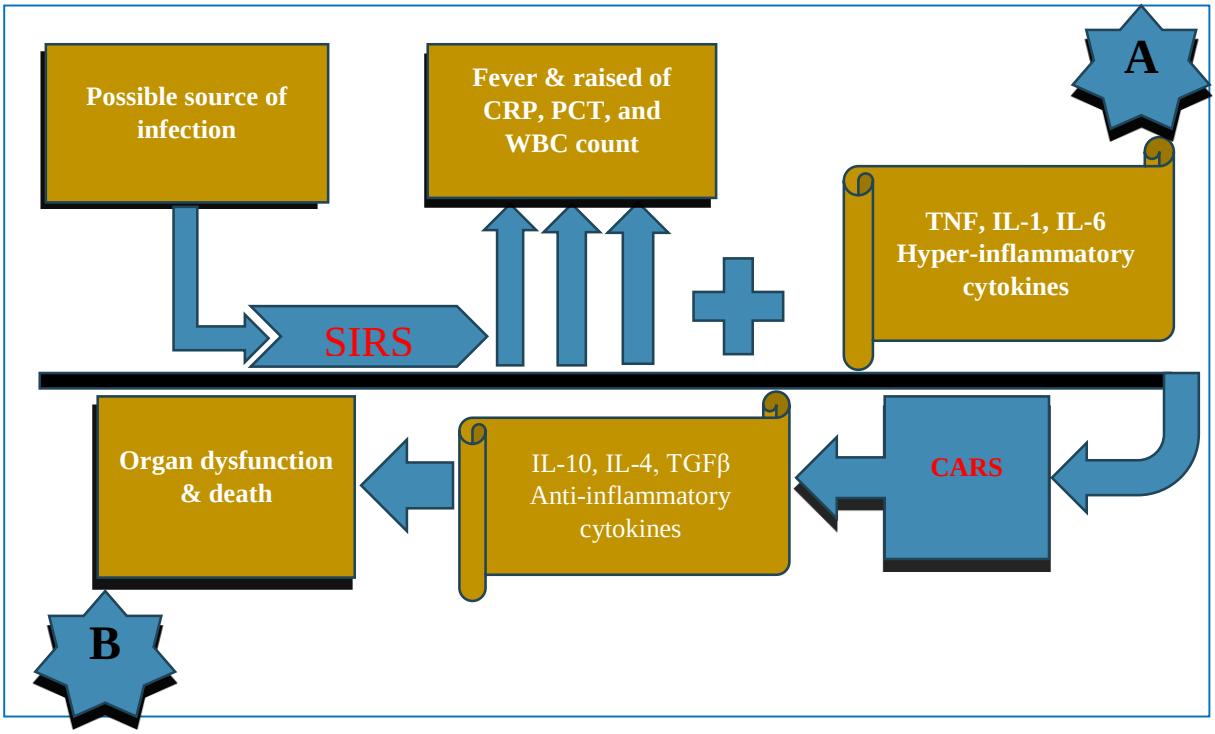
1 as an indicator for the onset of sepsis, and the majority of them concluded that a high serum level of MCP-1 in adult individuals indicates the existence of sepsis related to specific infections [52, 53]. However, there has been no single effective prognostic biomarker for sepsis to be used alone in the clinical field. As a result, of that, more than one biomarker must be used, including screening (CBC, LDH, and CRP), and diagnostic biomarkers (PCT, PTX3, PSN, and the values of MCP-1) in the hope of resolve and success to overcome the difficulties correlated with the diagnosis of sepsis. Early detection of the sepsis sources has a critical role in term of the minimize antibiotic abuse and misuse while also accelerating the healing from the infection.

3. Blood culture as a fundamental diagnostic method

A precise diagnosis of the bloodstream infections gives essential clinical data needed to identify and treat sepsis [54, 55]. Although, a blood culture alone is not sensitive enough to detect the causative agents of sepsis, is a precious tool and represents the gold standard method that is commonly used along with other complementary parameters for precise diagnosis [56].

However, in order to properly manage of sepsis in the medical setting, there are numerous essential guidelines to follow. One of the most important guidelines is to determine the infectious agents prior to starting antimicrobials wherever it is possible [57].

Figure 1.Show the development events of sepsis.



(A) Illustrates the early stage of sepsis, (B) represents the late stage.

Conclusions

The huge and dangerous consequences of sepsis episodes paid the research community to improve the strategies for early detection of actual causative agents.The proper identification is one of the most essential aspects since it allows rapid treatment and reduces mortality rates that may be evolved during the time of infection.In addition to the non-specific screening tests that are performed during infection,there are more specific medical laboratory criteria that can be used for early diagnosis, especially when the blood culture fails to detect the etiologic agent of sepsis while the patient exhibits clinical symptoms.In conclusion, while no single sepsis biomarker is perfect, many are useful in identifying severly ill patients who require

monitoring so that the condition can be detected and treated.

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