Biomarkers in Sepsis

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According to “Sepsis-3” consensus, sepsis is a life-threatening clinical syndrome caused by a dysregulated inflammatory host response to infection. A rapid identification of sepsis is mandatory, as the extent of the organ damage triggered by both the pathogen itself and the host’s immune response could abruptly evolve to multiple organ failure and ultimately lead to the death of the patient.

Keywords: sepsis ; biomarker ; procalcitonin ; Presepsin ; C-Reactive Protein

1. Introduction

Sepsis is a life-threatening clinical syndrome caused by a dysregulated host inflammatory response to infection, often associated with multiple organ dysfunction syndrome and death [1]. It is recognized as a leading cause of death worldwide, as highlighted by the Global Burden of Disease, which estimated 48.9 million incident cases in 2017, accounting for 19.7% of all global deaths [2]. The economic and health burden of sepsis worldwide is alarming; mortality in sepsis patients has been estimated to be ≥10%, rising above 40% when evolving to septic shock [1]; in 2011 the total sepsis-related costs for US hospitals accounted for more than US $20 billion [1].

The definition of sepsis has undergone several revisions over the years because of the highly variable clinical spectrum: the 2001 American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference Committee criteria for the host systemic inflammatory response syndrome (SIRS) are currently outdated because of their demonstrated poor ability to discriminate between different degrees of clinical severity [3]. Reassessment of these criteria in a clinical setting has shown that they are often found in many inpatients, including those who are noninfectious and who do not proceed to adverse outcomes [3]. The latest definition of sepsis, named “Sepsis-3”, was proposed in 2016 by the SCCM and the European Society of Intensive Care Medicine (ESICM) [1]. According to the SCCM/ESICM, sepsis is defined as a life-threatening organ dysfunction (ascertained as acute change in Sepsis-related Organ Failure Assessment (SOFA score) total score ≥2) “due to a dysregulated host response to infection” [1]. Septic shock is defined as a “subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities substantially increase mortality” [1].

Rapid detection of sepsis is mandatory since the patient’s overall clinical impairment and degree of organ damage are triggered by an extremely complex chain of events involving the recognition of pathogen-associated molecular patterns (PAMPs) of microorganisms by the host immune system [4]. As happens in other acute pathologic conditions such as acute encephalitis [5], but also in several diseases not directly provoked by an infection such as ischemic stroke [6][7][8], atrial fibrillation [9], and many others [10], the characteristics of the interaction between host and pathogen fundamentally affect the degree and severity of the systemic involvement of the patient. The damage-associated molecular patterns (DAMPs) released by the spillover from the injured cells [11] can result in an escalating state of inflammation that can abruptly lead to multiple organ failure (MOF) and can result in death. The prompt initiation of a broad spectrum empirical antibiotic therapy and patient-driven supportive strategies such as fluid resuscitation optimize outcomes. The so-called early goal-directed therapy in the first hour of documented hypotension leads to a 79.9% survival rate, each hour of delay being associated with an average decrease in survival of 7.6% [12]. Despite the development of bedside screening tools to facilitate the early detection of septic patients, a tool to which a definitive diagnostic value can be attributed is still missing, thus the diagnosis is today still challenging, and it continues to depend on the clinical judgment based on nonspecific clinical and laboratory variables. In addition, rapid discrimination between infectious and noninfectious causes presents a daunting challenge. The diagnosis of systemic infection is mainly based on direct microbiological tests such as cultures or polymerase chain reaction-based methods or indirectly using specific immunoglobulin dosage. Unfortunately, microbiology results often take several days to became positive and are not diagnostic in patients with ongoing infection in up to one-third of cases, especially if cultures were collected when antibiotic treatment had already been started [13].

Since the combined sensitivity and specificity of actual biomarkers (e.g., C-reactive protein (CPR), Procalcitonin (PCT) and Interleukin-6 (IL-6)) do not allow for the rapid ascertainment of the diagnosis [14][15] and sepsis-related adverse

outcomes rise with every hour of delay of proper intervention, new early biomarkers are urgently needed.

There is a growing amount of data about non-codingRNA, a group of transcripts that do not code proteins at first deemed as redundant RNAs but lately described as highly conserved transcripts involved in gene expression regulation through the modulation of chromatin rearrangement, histone modification, alternative splicing regulation and many other biological processes [16]. Recent findings speculate that circularRNAs (circRNAs), a particular type of long non-codingRNAs (lncRNAs) distinguished by a covalently closed-loop structure with neither 5′ to 3′ polarity nor polyadenosine tail, participates in gene regulation in a different way, regulating the microRNA (miRNAs) concentration in body fluids by competing with several miRNAs and regulating the downstream of messenger RNAs (mRNAs) [17].

Further demonstrating the increasing biological value that non-coding RNAs are proving to have, they seem to play a role in the pathogenesis of different diseases [18], and, given the complex interweaving between circRNAs, miRNAs, lncRNAs and mRNAs, various studies have addressed the issue of their role as novel diagnostic markers and therapeutic targets in many pathologic conditions including sepsis [19][20][21][22][23][24][25].

2. Role of Biomarkers in Sepsis

According to the Biomarkers Definitions Working Group, a biological marker or biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” [26].

A biomarker finds application across four domains or functional classes:

- As a diagnostic tool, i.e., a biomarker able to confirm a disease;
- As a tool able to stage or to stratify disease severity;
- As a prognostic tool;
- An effective tool for prediction and monitoring of clinical response of an intervention [26].

Biomarkers of sepsis hold the promise of closing the gap in obtaining mycobacterial cultures by providing clinicians with clinically useful data. There is a strong demand for new and accurate sepsis biomarkers, especially in the era of personalized medicine in which physicians must increasingly tailor clinical and therapeutic management to each patient. In the following part, without aiming to address this topic comprehensively, the role of some of the major biomarkers currently used in sepsis will be analyzed by discussing the merits and demerits of their use during the management and treatment of such a serious disease that has its cornerstone in the timeliness of identification and early and appropriate intervention.

2.1. C-Reactive Protein (CRP)

C-Reactive Protein (CRP) is a plasma protein belonging to the group of the so-called acute phase reactants which may increase rapidly during inflammatory conditions or secondary to non-specific acute inflammatory stimuli [26]. The acute-phase proteins are produced in the liver during inflammatory states under the control of cytokines: CRP is mainly synthesized through Interleukin-6 (IL-6) and Interleukin-1β (IL-1β) stimulation via the transcription factors STAT3 and NF-κB [27]. CRP, as a component of the innate immune system, during infection may recognize various pathogens associated molecular patterns (PAMPs) such as phospholipid fragments released from damaged cells consequently activating the complement system and finally inducing the death of the targeted cells [28]. CRP is released into the bloodstream after 4–6 h after an inflammatory stimulus and a plasma peak is reached in 36 to 50 h [14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29]. Several conditions besides infection can result in the elevation of the CRP-serum level [30]; a meta-analysis of Simon et al. [31] demonstrated a sensitivity of 75% [95% CI: 62–84%] and a specificity of 67% [95% CI: 56–77%] for CRP in differentiating bacterial infection from the noninfective cause of inflammation.

Liu et al. [32], in a systematic review and meta-analysis including 45 studies and 5654 patients, showed an acceptable level of sensitivity of 75% (95% CI: 69–79%) but a weak level of specificity of 67% (95% CI: 58–74%) for the ability of CRP to differentiate patients with sepsis vs. non-infectious inflammatory state/disorders. Tan et al. [33], comparing the ability of CRP and PCT to serve as biomarkers for sepsis diagnosis show similar sensitivity (CRP: 80%, 95% CI: 63–90%, procalcitonin: 80%, 95% CI: 69–87%) but significantly lower specificity for CRP (61%; 95% CI: 50–72%) than procalcitonin (77%; 95% CI: 60–88%) [33]. A possible explanation for the lower diagnostic accuracy of CRP as a sepsis biomarker (low specificity and moderate sensibility) could account for the slow-release kinetics as a consequence of the inflammatory

stimulus and its increase also due to other pathological conditions besides infections (e.g., trauma, burns, surgery or various immune-inflammatory conditions [34][35].

Finally, the limits showed that CRP remains a widely used diagnostic and therapeutic biomarker in sepsis to date, mainly because a decrease in its values correlates with the success of antimicrobial treatment [36].

2.2. Procalcitonin (PCT)

Procalcitonin is the precursor of calcitonin, released by the C-cells of parathyroid glands. Assicot et al. [37] in 1993 for the first time described the association between PCT serum levels and severe bacterial infection. Compared to CRP, the PCT has a better kinetic profile, increasing within 3–6 h after the onset of infection reaching its serum peak after 6–8 h [29]. Several studies investigated the diagnostic performance of PCT. A meta-analysis of Uzzan et al. [35], including studies from 1996 to 2004, showed a higher accuracy of PCT levels than CRP levels for the diagnosis of sepsis (Global diagnostic accuracy odds ratios: CRP 5.43 [95% CI: 3.19–9.23] vs. PCT 14.69 [95% CI 7.12–30.27] [35]. However, the authors included a restricted cohort study based only on surgery or trauma patients, and thus the conclusion cannot be extended to patients other than surgical conditions [35].

Tang et al. [38], in a meta-analysis of 18 studies, pointed out that PCT was not adequate in discriminating between sepsis and SIRS (both sensitivity and specificity were 71% [95% CI: 67–76] and the Area Under the Summary Receiver Operator Characteristic Curve was 0.78 [95% CI: 0.73–0.83] [38]. Another meta-analysis of 30 observational studies evaluating 3244 mixed subjects (pediatric and adult patients admitted in the Intensive Care Unit or Emergency Room), has given the PCT a sensitivity of 77% [95% CI: 72–81%] and a specificity of 79% [95% CI: 74–84%], with AUC 0.85 [95% CI 0.81–0.88] for accuracy in discriminating sepsis from a non-infectious state [39].

Several studies have also confirmed the clinical utility of PCT in driving antimicrobial therapy surveillance and the eventual de-escalation of antibiotic treatment [14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29].

To date, there are no established cut-off values of serum PCT concentrations that are able to discriminate sepsis versus septic shock [29].

2.3. Presepsin

Presepsin, the N-terminal fragment of 13 kDa of the sCD14 (the soluble form of the receptor of lipopolysaccharide-lipopolysaccharide binding protein), is an emerging biomarker and early indicator of bacterial infections [40]. Presepsin, as part of the Toll-like receptor group, takes part of the innate immune system, binding several pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS) of Gram- or peptidogligans [40]. In recent years, sCD14 has become one of the most widely sepsis biomarkers studied: the level of sCD14 increased significantly in patients with sepsis and septic shock compared with healthy people, and the change was significantly related to the severity and prognosis of the disease [29][41][42][43][44]. The diagnostic power of presepsin in detecting sepsis showed with a pooled sensitivity of 77–86% and a specificity of 73–78% [41][42][43][44]. Nevertheless, presepsin still needs wider investigation and further validation and comparison with standard sepsis biomarkers prior to being recommended for the hospital-setting.

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