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New sepsis biomarkers

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ABSTRACT

Sepsis remains a leading cause of death in the intensive care units and in all age groups worldwide. Early recognition and diagnosis are key to achieving improved outcomes. Therefore, novel biomarkers that might better inform clinicians treating such patients are surely needed. The main attributes of successful biomarkers would be high sensitivity, specificity, possibility of bedside monitoring and financial accessibility. A panel of sepsis biomarkers along with currently used laboratory tests will facilitate earlier diagnosis, timely treatment and improved outcome may be more effective than single biomarkers. In this review, we summarize the most recent advances on sepsis biomarkers evaluated in clinical and experimental studies.

1. Introduction

The first scientific definition of sepsis proposed by Schottmuller in 1914 was that sepsis is a state caused by microbial invasion from a local infectious source into the bloodstream which leads to signs of systemic illness in remote organs [1,2]. In 1992 at the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine, sepsis was defined as the host's immune response [systemic inflammatory response syndrome (SIRS)] to injury and/or infectious stimuli in the presence of a known (or strongly suspected) infection [3]. The same consensus group also defined criteria to qualify SIRS, which schematized the host inflammatory response to infection, trauma, ischemia-reperfusion injury and burns. Moreover, in 2001, this same conference modified the SIRS definition by expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience [4]. Sepsis remains a leading cause of death in the intensive care units and in all age groups worldwide. In Europe, every year, 157 000 people die for this systemic multi-organs failure as a consequence of bacterial or fungal infection [5].

The septic response is an extremely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions and circulatory abnormalities [6,7]. The incidence of sepsis is increasing due to multiple factors, including the aging of the population, the performance of more invasive procedures and the continuing emergence of antibiotic-resistant microorganisms [8]. In some cases, the diagnosis is challenging. An early diagnosis of sepsis helps to enable rapid treatment, improve outcomes and reduce unnecessary antibiotic therapy. Diagnostic biomolecular markers could greatly simplify, accelerate and objectify the entire healing process, from diagnosis and process monitoring to verification and timely correction of therapy. At present, there is no ideal and clinical gold standard for the diagnosis of sepsis, as microbiology is not sensitive enough and laboratory tests are unspecific for use as a reference standard [9–11].

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Biomarkers can have an important role in this process because they can indicate the presence or absence or severity of sepsis and have the potential to serve a crucial role by providing adjunctive information to guide clinicians to rapid diagnosis and extension of treatment beyond the standard therapy [12,13]. This review will discuss the major biomarkers of sepsis.

2. Sepsis biomarkers

Biomarkers are a valuable tool in facilitating early diagnosis, identification of patients at high risk of complications and in monitoring disease progression. These assessments are critical for establishing an appropriate therapy and improving patient outcomes. An ideal biomarker provides indirect but ongoing information (determinations) of disease activity.

In 2010, Pierrakos and Vincent estimated that at least 178 different sepsis biomarkers have been reported in the literature [14]. Five years later, that number is likely higher.

3. Plasma chitotriosidase (ChT) activity

ChT, a member of the mammalian chitinase family, structurally homologous to chitinases from other species, is synthesized and secreted by specifically activated macrophages. ChT was found to be an excellent marker for lipid laden macrophages in Gaucher patients and is now widely used to assist clinical management of patients [14,15]. Moreover, an increased ChT has been noted in other inherited lysosomal storage disorders including atherosclerosis, malaria, hematological disorders and other conditions where activated macrophages are involved [15–17]. ChT was previously proposed to quantify the severity of sepsis. In a complex surgical case, with prolonged sepsis and consistently high ChT, it was found that the least increased values occurred in stages of extreme illness, with profound hypocholesterolemia.

ChT in sepsis should be better characterized, correlated to other biomarkers and to clinical events before becoming a reliable biomarker of septic evolution that could be implemented for patient management and decision process [18].

4. Presepsin

Presepsin is a novel promising marker for diagnosing and monitoring sepsis. Presepsin is a 13-kDa protein that is the truncated N-terminal fragment of cluster of differentiation 14 (CD14), the receptor for lipopolysaccharide (LPS)/LPS binding protein complexes. CD14 activates the toll-like receptor 4 proinflammatory cascade in the presence of infectious agents. Two forms of CD14 are membrane CD14 and soluble CD14 (sCD14). Complex LPS–LPS binding protein-CD14 is shed into the circulation and plasma protease generates sCD14 molecule called sCD14 subtype-presepsin. Presepsin is generated as the body response to bacterial infection and its production is induced by phagocytosis of bacteria. So, the level of presepsin should reflect the severity of infection rather than the degree of inflammation [19,20]. Some clinical studies showed that level of sCD14 increased in septic patients and it is not significantly different between patients with Gram-positive and Gram-negative infection [21–25]. This biomarker shows high specificity, and results from experimental and clinical studies are reinforcing the proof of concept [26]. Presepsin appears to be the most promising new biomarker for early diagnosis of sepsis and a better prognostic biomarker than procalcitonin.

5. Interleukin (IL)-27

A revision of the literature showed that ILs have been long investigated as potential biomarkers of sepsis. For instance, IL-6 has been evaluated as biomarker of the severity of sepsis. A recent study pointed out that IL-27 could be used as novel biomarker of sepsis in critically ill children [27].

IL-27 was first discovered in 2002 as a new member of the IL-12 cytokine family [28]. IL-27 is a heterodimeric cytokine produced by antigen presenting cells upon exposure to microbial products and inflammatory stimuli [29,30].

In a recent study, Hanna *et al*. showed that IL-27 may serve as a useful biomarker in estimating risk of bacterial infection among critically ill paediatric patients with bloodstream infections [31]. In particular, among those classified as immune-compromised, this diagnostic biomarker may be useful either alone or using a combination strategy with other available biomarkers. So, although further research is warranted, IL-27 exhibited high specificity and positive predictive values for bacterial infection in critically ill children. It has been also demonstrated that a combination of IL-27 and procalcitonin (PCT) improves the overall ability to predict infection, compared with that of either biomarker alone.

6. Hepcidin

Current research has expanded the diagnostic implications of hepcidin in other medical conditions, especially hepcidin is indicated as a potential acute-phase biomarker in inflammation and sepsis. Hepcidin is a novel peptide hormone of hepatic origin and it has a crucial role in iron metabolism interfering with the access of microorganism to iron. The synthesis of hepcidin in the liver is induced by IL-6 in response to inflammation and abnormal serum levels have been observed in different diseases and sepsis [32,33]. Recently, Cizmeci *et al*. showed that hepcidin is a reliable biological marker of early-as well as late-onset sepsis in neonates [34]. The serum hepcidin values were in keeping with the disease process in late-onset neonatal sepsis. A four-fold rise of serum hepcidin during sepsis returned to normal levels following therapy suggesting its use as marker of late-onset neonatal sepsis [35].

7. Macrophage migration inhibitory factor (MIF)

MIF is a pleiotropic immune regulatory cytokine whose effect on arresting random immune cell movement was already recognized decades ago. Multiple studies have pointed to the utility of MIF as a biomarker for different diseases that have an inflammatory component and these include systemic infections and sepsis, cancer, autoimmune diseases as well as different metabolic disorders. MIF has a chemokine-like function and promotes the directed migration and recruitment of leukocytes into infectious and inflammatory sites [36]. MIF is produced by a variety of cell types in addition to immune cells such as monocytes/macrophages, B- and T-cells including endocrine, endothelial and epithelial cells [37]. It is rapidly released in response to stimuli such as microbial products, proliferative signals and hypoxia [38]. Some studies showed that MIF

plasma concentrations can be elevated in patients with severe sepsis when compared to healthy control individuals [39–44]. A study conducted by Gando *et al*. showed that elevations of MIF and tumor necrosis factor-α were both related to poor prognosis and mortality in patients with intravascular disseminated coagulation with systematic inflammation compared to non-intravascular disseminated coagulation patients [45]. However, when compared to other infectious biomarkers, MIF had a limited value as single marker compared to C-reactive protein (CRP) or PCT, which exhibited superior diagnostic characteristics [45]. So, MIF seems to have a greater diagnostic value when used in combination with other biomarkers rather than alone. This observation is in line with another study where the high measured levels of MIF and PCT correlated with lethal outcome in severe burned patients [46].

8. Conclusions

Several potential biomarkers of sepsis and inflammation have been identified and investigated in recent years, but none of them has sufficient specificity or sensitivity to characterize by itself the presence of an infection and the complexity of the inflammatory and immune processes involved, and therefore to be routinely employed in clinical practice. A combination of several sepsis biomarkers may be more effective.

Conflict of interest statement

We declare that we have no conflict of interest.

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