## Editorial

Aldo Clerico and Mario Plebani

# Biomarkers for sepsis: an unfinished journey

In 1992, an expert panel from the American College of Chest Physicians and the Society of Critical Care Medicine [1] produced a consensus statement focused on the definitions for sepsis and organ failure. Indeed, the term sepsis has long been used interchangeably with bacteremia, severe sepsis, or even septic shock, causing some confusion and difficulty in comparing results from different studies [2]. This consensus document stated for the first time the definitions and criteria with the aim to distinguish between infection, bacteremia, systemic inflammation response syndrome (SIRS), sepsis, severe sepsis, septic shock, and sepsis-induced hypotension (Table 1). The clinical presentation of sepsis in adults can be hardly distinguishable from other non-infective conditions, which share a systemic inflammatory response and are collectively named SIRS [2, 3]. From a clinical point of view, it is important to note that, although SIRS and sepsis have similar clinical presentation, these two conditions can require different treatments. Indeed, sepsis always requires antibiotic therapy optimized with regard to the choice of specific agent(s); conversely, antibiotic treatment may be contraindicated for some clinical conditions related to SIRS [3].

Sepsis is still a relevant clinical problem. The prevalence of SIRS is very high, affecting one third of all in-hospital patients and >50% of all patients on intensive care unit (ICU); in surgical ICU patients, SIRS occurs in >80% patients [2]. In such patients, sepsis evolves to severe sepsis in >50% of cases, whereas the evolution to severe sepsis in non-ICU patients is ~25% [2]. Severe sepsis and septic shock occur in 2%–3% of ward patients and 10%–15% of ICU patients, and 25% of patients with severe sepsis suffer from septic shock [2].

Sepsis is a leading cause of mortality in critically ill patients [3, 4], with a mortality risk ranging from 40% to 70%, and septic shock is the most common cause of death in the modern ICU [3]. Considering that the delay in the diagnosis and initiation of antibiotics has been shown to increase mortality in septic patients [3], the ability to accurately distinguish between SIRS and sepsis has become one of the most important goals in medicine [4]. Unfortunately, there is no "gold standard" for the diagnosis of sepsis. As a result, it is not surprising that there is a considerable debate regarding the search of reliable biomarkers to achieve this goal.

From a clinical viewpoint, a reliable biomarker for sepsis should improve the diagnosis, risk stratification, and/or therapeutic decision-making in septic patients. Then again, from a pathophysiologic viewpoint, a validated group of biomarkers promise to transform sepsis from a pathophysiologic syndrome to a group of distinct clinical disorders [5]. Unfortunately, there is a plethora of biomarkers proposed in this field, thus suggesting that a reliable biomarker for sepsis has never been found [4–8]. Indeed, the complex pathophysiology of sepsis involves many active substances (such as cellular mediators, neuro-hormones, or cytokines), which are related to coagulation, complement activation, inflammation, apoptosis, and many other cellular and tissue effects. Moreover, the systemic nature of sepsis, which involves multiple organs, can trigger the release of several tissue-specific biomarkers, even including the cardiospecific biomarkers, brain natriuretic peptide (BNP), and cardiac troponins [9–11].

In this issue of *Clinical Chemistry and Laboratory Medicine*, Di Somma et al. [12] provide an overview about the potential clinical usefulness of some biomarkers of sepsis. This opinion article represents a synopsis of the lectures on biomarkers and sepsis of the Third Italian GREAT Network Congress, which was held in Rome, 15–19 October 2012. In ref. [12], the authors discuss not only the biomarkers already standardized and actually used in clinical practice but also some biomarkers that are still tested for experimental use.

According to ref. [12], the rapid diagnosis of sepsis in emergency departments is often difficult because the symptoms are rather not specific. Among the huge number of biomarkers proposed [4–8, 12], only procalcitonin (PCT) complies with most of the desirable preanalytical, analytical, and postanalytical features for an ideal laboratory biomarker (Table 2). Indeed, PCT can be assayed by means of sensitive and precise immunometric methods using several automated platforms, which allow the measurement of serum PCT with a turnaround time compatible with the rapid diagnosis indispensable in the emergency department [13–15]. Moreover, some recent systematic review and meta-analyses, including also an economic evaluation, indicated that PCT-guided antibiotic therapy is associated with a reduction in antibiotic therapy that, under certain assumptions, may reduce the overall costs of care [16–18]. Another meta-analysis [19], involving 1959 neonates, evaluated the

| Term | Definition and criteria |
|---|---|
| 1. Infection | Inflammatory response to the presence of microorganisms or invasion of normally sterile tissue by these organisms |
| 2. Bacteremia | Presence of viable microorganisms in the blood |
| 3. SIRS[a] | Two or more of the following:<br>– Temperature >38°C or <36°C<br>– Heart rate >90 bpm<br>– Respiratory rate >20 bpm or $PaCO_2$ <32 mm Hg<br>– White blood cell count >12,000/mm$^3$ or <4000/mm$^3$ or >10% band forms |
| 4. Sepsis (=1+3) | Systemic response to infection |
| 5. Severe sepsis | Sepsis and organ dysfunction, hypoperfusion, or hypotension<br>Manifestations of hypoperfusion may include but are not limited to<br>– Lactic acidosis<br>– Oliguria<br>– Acute alteration in mental status |
| 6. Septic shock (=5+7) | Sepsis-induced hypotension, persisting despite adequate fluid resuscitation and manifestations of hypoperfusion as listed in 5[b,c] |
| 7. Hypotension, sepsis-induced | A decrease in systolic blood pressure to <90 mm Hg, or >40 mm Hg from baseline, in the absence of other cause for hypotension[c] |

**Table 1** Definitions for the septic syndromes adapted from the American College of Chest Physicians/Society of Critical Care Medicine expert panel [1] and reference [2].

[a]SIRS may be caused by a variety of insults in addition to infection, including but not limited to trauma and status postmajor surgery, acute pancreatitis, and burns. [b]An adequate fluid challenge is usually considered as at least 500 ml fluid infused rapidly and persisting hypotension as one persisting for >1 h. [c]Patients on inotropic/vasoactive agents may not be hypotensive at time of evaluation.

specific setting of neonatal sepsis reporting that serum PCT at presentation presents a very good diagnostic accuracy (area under the curve=0.87) for the diagnosis of neonatal sepsis. However, in view of the marked observed statistical heterogeneity, along with the lack of a uniform definition for neonatal sepsis, the interpretation of these findings should be done with appropriate caution [19].

Cardiac dysfunction is a common complication of severe sepsis and septic shock; approximately 50% of patients with severe sepsis and septic shock seem to have any form of impairment of the left ventricular systolic function [9, 20]. Mortality from severe sepsis or septic shock

– Acceptable to patient
– Stability in vivo and vitro
– Adequate analytical sensitivity (functional sensitivity)
– Good degree in reproducibility and accuracy
– Easy to perform
– Short analytical turnaround time
– Complete automation of assay
– International standardized
– Low cost
– Low biological variation
– Reference range and cutoff values tested for gender, age, and ethnicity dependence
– Good diagnostic and prognostic accuracy
– Favorable cost-benefit ratio

**Table 2** Desirable preanalytical, analytical, and postanalytical features of an ideal biomarker.

ranges from 30% to 60%, with only a minor decline in mortality over the last decades despite the aggressive treatment and the enormous costs invested in the ICUs [20]. As a result, the early recognition of myocardial dysfunction is crucial for the administration of the most appropriate therapy [9, 20]. Cardiac troponins I and T and B-type-related natriuretic peptides (i.e., BNP and NT-proBNP) are the biomarkers recommended for the early and accurate detection of cardiac damage and myocardial dysfunction, respectively [21]. Several recent studies confirmed that the measurement of cardiac troponins and B-type-related natriuretic peptides could be useful in septic patients [9–11, 22–25]. These biomarkers are usually elevated in patients with septic shock [9–11, 21–25] and predict an adverse outcome, especially natriuretic peptides [11, 22, 24, 25]. Moreover, monitoring BNP in early sepsis to identify occult systolic dysfunction might prompt the earlier use of inotropic agents [23].

Acute kidney injury (AKI) is frequently observed with an incidence ranging from 20% to 25% and a high mortality risk (approx. 70%) in patients with severe sepsis [12, 26]. From a clinical point of view, it is important to note that the serum creatinine is unable to rapidly recognize AKI, because it rises slowly and reaches a steady state when the process of AKI has already initiated, so that there is compelling need for faster and more specific biomarkers [27]. Many biomarkers have been suggested for an accurate and early detection of AKI, but only neutrophil gelatinase-associated lipocalin (NGAL), especially if assayed in urine

rather than in blood samples, is the most likely biomarker to be integrated into clinical practice in the near future [12, 26, 27]. According to Di Somma et al. [12], NGAL is increased in patients with sepsis, but its specific role in this condition is still controversial due to the potential confounding factor of extrarenal source of production [26–29]. It should therefore be considered as a complementary marker during the course of sepsis for the diagnosis of AKI, helping PCT to manage the septic process.

Considering future remarks, Di Somma et al. [12] discuss in detail the other possible biomarkers for sepsis, including adrenomedullin and midregional proadreno-medullin, some tyrosine kinase receptors (such as Mer receptors), and thrombopoietin. Among these novel bio-markers, the measurement of ADM with new highly sensitive immunoassay methods is suitable for routine use and can serve as a tool for the therapy monitoring in septic patients [30]. In addition, the immature granulocyte count and the granulocyte maturation index may improve the early diagnosis of septic state [31–33].

At present, the combination of newer and older and well-known sepsis biomarkers (such as red blood cell distribution width), used as a multimarker approach, may be useful for emergency physicians to promptly identify sepsis and improve the diagnosis, identification of organ dysfunction, treatment, and risk stratification. Despite major promises, however, all the steps of the translation process need to be respected and robust evidence should be collected to demonstrate unquestionable favorable health impacts of these new biomarkers before their introduction in clinical practice.

## Conflict of interest statement

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**\*Corresponding author: Prof. Mario Plebani**, Department of Laboratory Medicine, University-Hospital of Padova, 35128 Padova, Italy, Phone: +39-0498212792, Fax: +39-049663240, E-mail: mario.plebani@unipd.it

**Aldo Clerico:** Department of Laboratory Medicine, Fondazione Regione Toscana G. Monasterio and Scuola Superiore Sant'Anna, Pisa, Italy