Editorial

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"Personalized" sepsis care with the help of specific biomarker levels on admission and during follow up: are we there yet?

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The recognition over 25 years ago that the host response plays an exquisite role in systemic infections and sepsis led to the current standard sepsis definition. Unfortunately, the systemic inflammatory response syndrome (SIRS) criteria turned out to be less useful than anticipated, lacking sensitivity, specificity, and ease of clinical application [1]. Had some of the novel host-response biomarkers been available then, it arguably would have been preferable to white blood cell (WBC) count as a laboratory-based SIRS criterion, considering the greater sensitivities and specificities for diagnosis of sepsis and provision of prognostic information demonstrated in a growing body of literature linking novel inflammatory markers to the presence and severity of sepsis [2]. Specific sepsis biomarkers have the ability to improve early sepsis recognition and severity assessment and may also help to guide therapeutic decisions in individual patients, particularly when measured serially. Thereby, measurement of initial and follow-up biomarkers potentially allows transition from bundled sepsis care to more individualized, "personalized" sepsis management in single patients. In this issue of *Clinical Chemistry and Laboratory Medicine* (*CCLM*), several original research papers provide novel insight into kinetics of inflammatory biomarker in different settings and patient population, thereby importantly advancing the field of biomarker research.

Among these emerging inflammatory sepsis markers, procalcitonin (PCT) is a promising candidate. PCT is upregulated by microbial toxins and certain pro-inflammatory mediators and is downregulated as these substances subside during recovery. PCT expression is attenuated by the cytokines typically released in response to a viral infection (e.g., interferon γ) [3]. PCT measurements may therefore be helpful in estimating the risk for sepsis, its course, and efficacy of sepsis treatments. Yet, there is an ongoing debate whether or not PCT provides more useful prognostic information, also in regard to cost-effectiveness, compared with more traditional markers such as reactive protein as well as WBC count.

Herein, a secondary analysis from a prospective study with 925 community-acquired pneumonia patients provides interesting novel results by comparing the prognostic potential of PCT, C-reactive protein (CRP), and WBC, both on admission and during follow-up in regard to mortality and treatment failure [4]. PCT, CRP, and to a lesser degree WBC provided prognostic information, particularly when considering their kinetics at days 5 and 7 and when looking at adverse clinical outcomes instead of mortality alone. Importantly, kinetics of PCT and CRP also improved routinely recommended clinical risk scores – such as CURB65. Whether such combinations, however, will change management of patients and thereby potentially reduce length of hospital stay could not be answered by this study.

Regarding the kinetics of inflammatory markers, a study authored by Dr. Hoffmann and colleagues describe in great depth the dynamics of four established markers (PCT, CRP, WBC, thrombocyte counts) and two novel potential markers (granularity index, δ-hemoglobin) during the onset and resolution of a high-grade inflammation over a time period of 168 h in more than 1000 patients [5]. The study illustrates the different trajectories of the markers and the importance of blood sample timing in regard to the interpretation of results.

Another interesting sepsis marker is presepsin, the fragment of soluble CD14, which consists of 64 amino acid residues and originates from the cleavage of the CD14 on the membrane surface by cathepsin and other lysosomal enzymes [6]. The study authored by Dr. Sargentini focused on a cohort of 21 critically ill, septic patients who showed a relapse of disease after initial resolution of illness. The authors found that both presepsin and PCT allowed differentiation of healthy controls and septic patients with very high accuracy (area under the curve, 0.89 and 0.91); yet in patients with relapse of sepsis, PCT levels normalized during the transient remission period whereas presepsin

levels remained elevated. The study thus suggested that the combined use of these markers may allow early identification of relapse, which has important clinical consequences in regard of early discharge and frequency of monitoring patients.

A similar conclusion was also drawn by a Korean study authored by Jekarl and colleagues where PCT, interleukin (IL) 6, and CRP had a high diagnostic yield for infection diagnosis [7]. Also, PCT, IL6, and IL5 had prognostic value and correlated with severity of sepsis. Finally, interferon (INF) γ had an inverse relationship with severity of sepsis. Again, this study emphasized the benefit of biomarker bundles for improved management of sepsis patients.

Although these markers may be influenced by trauma and surgical stress, the marker kinetics may still provide important clinical information. A study authored by Dr. Kyung Ran Jun and colleagues found that for the perioperative monitoring of patients, PCT showed good predictive accuracy for adverse outcomes with less influence from surgical trauma compared to CRP and other markers [8].

Another emerging biomarker for sepsis diagnosis is expression of CD64 on neutrophils (CD64 index). Dr. Rogina and colleagues found an excellent discriminatory value to predict sepsis as compared with other inflammatory markers in a cohort of 88 critically ill patients [9]. Although flow cytometer is needed for measurement of CD64 index, making it more expensive and laborious, the marker has high potential to improve sepsis diagnosis and management.

In regard to emerging technologies for PCT measurements, a study from Italy [10] evaluated the analytical performance of the novel diazyme PCT immunoturbidimetric assay on Beckman CoulterAU5800 as compared with the reference Kryptor technology. This novel technology has some technical and analytical advantages over Kryptor technology, including a lower volume of sample needed for measurements (i.e., 20 vs. 50 μL), a faster turnaround time (10 vs. 19 min), lower costs, as well as the high throughput. These benefits potentially make its availability more widespread to different clinical laboratories. The study results were promising, showing high agreement between both methods, particularly when PCT concentrations were >0.16 ng/mL.

Another study published in this issue of *CCLM* focused on potential cost savings associated with biomarker-guided care, namely PCT-guided antibiotic stewardship [11]. The study used data from a recent large individual patient data meta-analysis including all 14 published antibiotic stewardship trials and a total of 4221 participants [12]. The study was adapted to the US setting by applying the meta-analytic results to US lengths of stay, costs, and practice patterns and found substantial savings associated with the use of PCT-guided care in across different respiratory infections and common US treatment settings. Extrapolated to the overall US population, the study estimated total savings of $1.6 billion annually. Thereby, only direct costs associated with antibiotics and resource use was considered – and thus cost savings maybe even more extensive when considering also secondary effects such as reductions in antibiotic resistance and *Clostridium difficile* infections.

Today's available biomarker for sepsis diagnosis and prognostication are still far from being perfect. An overlap occurs in biomarker levels between SIRS patients with inflammation and no bacterial infection and patients with sepsis. This observation may partly relate to methodological difficulties in establishing a gold standard sepsis diagnosis in observational studies and to the heterogeneity of the types and severities of infections causing sepsis [11]. Yet, in addition to evaluating novel sepsis markers based on their ability to differentiate the sepsis syndrome using the arbitrary definition established many years ago, we should focus on the results of comparative effective research trials ultimately telling us whether or not a potential sepsis biomarker improves our ability to identify the at-risk population measured by clinical outcomes and antibiotic exposure. Among the different sepsis markers, PCT has been most thoroughly put on the spot, and results are encouraging [13]. Whether addition of other emerging markers can further improve these results should be investigated in future trials. The converging crises of increasing resistance and collapse of antibiotic research need urgent action. More widespread use of biomarker protocols is an evidence-based, first step to slow down the former trend while awaiting even more sophisticated biomarker algorithms in the long run.

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