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WHAT'S NEW IN INTENSIVE CARE

Why biomarkers failed in sepsis

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And yet at the present time the subject is by no means fully elucidated, and it is not even possible to give a general definition of the term septicaemia, which could correctly represent all the different conceptions of its nature current at the present time.

W. W. Van Arsdale (1886) [1].

Sepsis was described for the first time by Hippocrates in the fourth century B.C. as a decomposition of organic matter. Biomarkers have for more than a 100 years been used to assist clinicians in treatment decisions in sepsis [2]. Well aware that microbiological methods have considerable limitations in sensitivity, and in hyperacute settings like sepsis, that conventional culture growth has a considerable delay, clinicians have continued the search for a single efficient biomarker for managing sepsis. It is obvious to almost all researchers and clinicians that this approach has failed. A few hours of search using terms like [sepsis], [biomarker], and [accuracy] will convince that no single biomarker has shown especially high performance uniformly to diagnose sepsis, and additionally that certain biomarkers perform extremely differently according to the variety of factors and processes involved in sepsis.

What should biomarkers be used for in sepsis?

Syndrome recognition and precise diagnosis

When characterizing sepsis with biomarkers, it is key to consider whether biomarker candidates can increase the clinician's insight into (1) the genetic and phenotypic diversity of human pathological bacteria; (2) the diverse human immunological response and the multitude of host responses to microbial invasion, with some key elements being pattern recognition, NF-κ-B activation, and release of pro- and anti-inflammatory mediators; (3) see ref. [3]; and (4) damage to the vascular endothelium [4], lung tissue [5], and other vital functions, activation of coagulation [6], stiffening and vulnerability of the small vessels (via increased NO release) and the red blood cells resulting in microcirculation breakdown in some patients [7]. Since host genetics is diverse, each of these processes can be highly differentiated from person to person [8]. Multiplying the diversity in each of the above steps gives an impression of the diversity of the course of serious human bacterial infections. No single biomarker can capture all this; future sepsis management will demand robust and validated biomarkers for each important part of the pathogenesis in severe human infection, and combinations of different biomarkers for potential organ dysfunction and biomarkers of infectious processes will facilitate the clinician's diagnostic decisions regarding anatomic source of the infection and thus of timely and correct treatment. Some target points for biomarker use in recognizing sepsis pathophysiology are displayed in Fig. 1.

Improving antibiotic stewardship

Different biomarkers can, according to the level of increase in sepsis patients, predict an increased probability that an antibiotic intervention may provide the patient with some benefit or not. Classic trials testing different strategies of antibiotic stewardship using this principle include the ProRATA trial [9] and the PASS trial [10]. The ProRATA trial tested, among critically ill patients, whether antibiotics could be discontinued whenever the level of polypeptide biomarker procalcitonin (PCT) was low or decreasing. This trial proved that the use of antibiotics in a population of septic shock patients could be reduced without any obvious harm; the main critique of this trial was the low algorithm adherence. The results from the ProRATA trial were recently confirmed in the SAPS trial [11]. In contrast, the PASS trial tested, also in critically ill patients, whether a lack of PCT decrease

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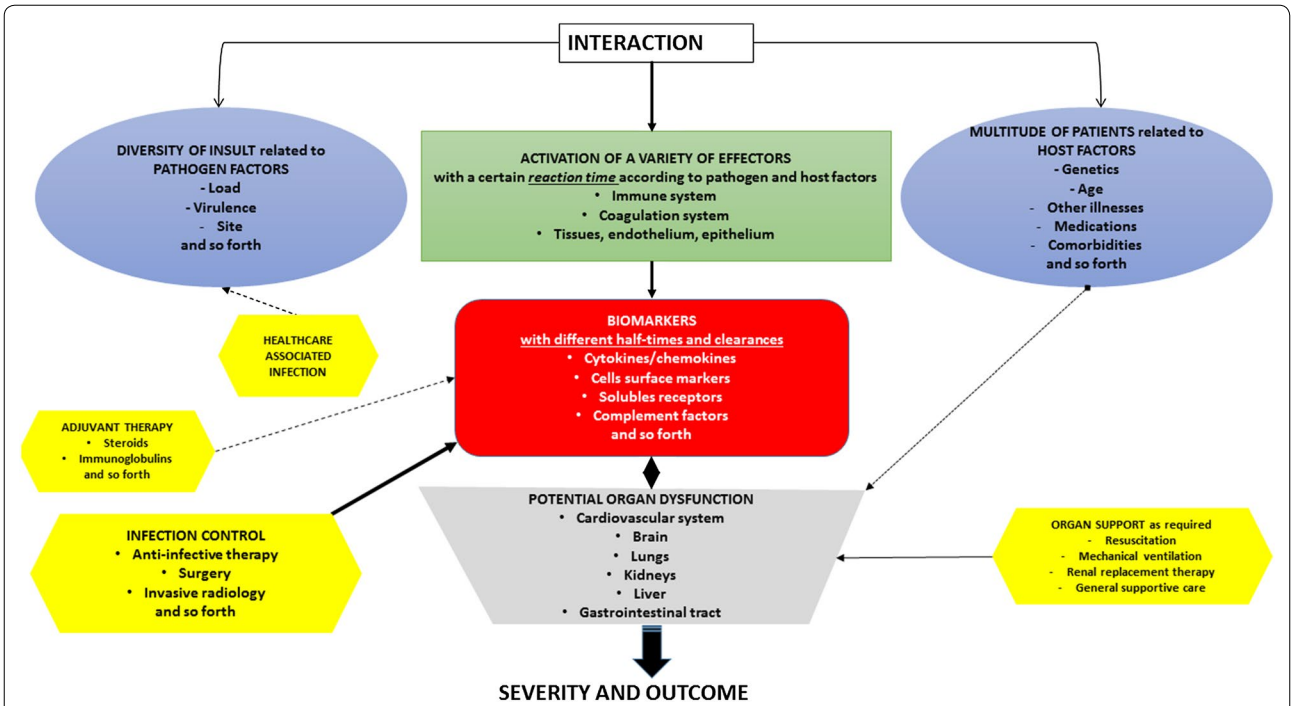

Fig. 1 Target points for biomarkers in recognizing sepsis pathophysiology

from the previous day was a signal that the infection was uncontrolled, and thus an increased probability that the patient would benefit from pre-emptive expansion of the microbial spectrum covered by the administered antibiotics. The trial failed to improve survival (primary endpoint). The trial used a dynamic cutoff based on day-to-day changes; it was criticized that the algorithm was uniform for surgical and medical patients, since the optimal cutoff does differ for these patient categories.

To give information on prognosis

Until now, prognostic biomarkers have mainly been used for overall prognosis. This adds information of how to stratify the observation level of patients. To aid clinicians in specific therapeutic decisions, more biomarkers should be validated to give information on immediate organ prognosis, thus providing patients with therapy targeted towards organ function preservation.

How should we move on?

First of all, when defining what we want from a new sepsis biomarker, it is important to consider whether the biomarker will increase the knowledge of core pathophysiological processes going on (or about to happen) and whether this knowledge can lead to a qualified and important change in therapy?

Second, classic diagnostic and prognostic biomarkers should be supplemented with biomarkers of core tissue functions, and genomic, proteomic, and metobolomic assays. As examples of biomarkers that give information on core tissue functions, markers of endothelial function and damage, Syndecan-1 and soluble thrombomodulin (sTM) can supply us with real-time information about the status of the glycocalyx of the endothelium and the more profound parts of the endothelium, respectively [12], hyaluronic acid may be useful in monitoring hepatic impairment in sepsis (own unpublished data), and surfactant protein D may offer useful information on the status of the alveolar epithelium [13]. This should be tested in a more systematic way. In particular, the issue of cut points for interpretation of biomarkers of sepsis should be given attention; biomarkers with varying optimal cut points in different sepsis populations may be of little use, since clinicians may be confused as to which cut point should be used in their own hospital.

Surveillance of different metabolic processes, hormone levels, and catabolic levels can probably be monitored in an advanced way by using state-of-the-art metabolomics assays; however, only few reports exist on this so far [14].

Third, as a relatively new option, differentiated characterization of infectious disease and host response can be supplemented by host genome sequencing in large sepsis cohorts and advanced interpretation models based on the clinical phenotypes characterized in these patients. Since sequencing methods are now adequate, rapid, and

within economic reach, the major challenge in this field is useful interpretation of the data from such analyses.

In conclusion, the term sepsis covers a wide variety of pathophysiological processes taking place in an infected individual, and which lead to a diversity of functional defects, cellular dysfunctions, and organ impairments. A magic bullet sepsis biomarker approach to capture all this in one marker should be abandoned in favor of research to uncover and quantify several important pathophysiological processes taking place in each infected patients with diverse metabolic profiles and different genetic risk profiles. With such information, it is more likely that individualized interventions targeted for the specific patient will be effective in improving prognosis and reducing harmful side effects from unnecessary therapy.

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Compliance with ethical standards

Conflicts of interest
Dr. Jensen reports that his institution received less than 2500 € from Thermo Fisher for a previous study of biomarkers of infection. Dr. Bouadma reports no conflicts of interest.

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