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WHAT'S NEW IN INTENSIVE CARE

Future of the ICU: finding treatable needles in the data haystack

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Sepsis in the ICU of the future

The identification of subtypes of disease with distinct clinical and biological features, divergent natural histories, and differential treatment responses has had a major impact on a variety of medical domains, ranging from oncology to infectious diseases. Nowadays, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. In this focus editorial we break down the need for an individualization of treatment into three axes: the infection (i.e., the pathogen), the host response and organ dysfunction (Fig. 1). The key message is that patients fulfilling the sepsis criteria are very dissimilar and that this heterogeneity results in non-superiority for almost every tested intervention. In the ICU of the future, sepsis will be classified based on treatable traits in these three dimensions. The biggest challenge of the coming decade is to make sense of huge datasets and to integrate epidemiological and biological data into a single perspective.

The pathogen: new gold standard tests?

Treatment of the causative pathogen is already pseudo-individualized in sepsis [2]. Antibiotic regimes are stratified by the most likely source of infection, whether the infection is community- or health-care acquired, the degree to which the host is immune-compromised and the local ecology.

With the development of culture-independent methods for pathogen detection and identification of antibiotic resistance, we are on the verge of true individual selection of antibiotics based on pathogen information rather than epidemiological considerations. Legionella and Pneumococcal urine antigen tests are already available in most clinics and act as an example.

The theoretical advantages of molecular methods, as compared to normal cultures, include a substantially shorter time for reporting the test result (both positive and negative) and the detection of DNA in the blood even after antibiotic administration, even when the pathogens are dead. This would in theory increase positive test results and thereby allow for earlier treatment of the causative pathogen. However, most molecular assays are biased towards common pathogens, and therefore it is uncertain whether broad-spectrum antibiotics can be withheld even with a positive test. Second, especially in patients with a low a priori likelihood on bacteraemia, molecular tests may yield false-positive results due to transitory bacteraemia without infection.

The challenge for the ICU of the future is to learn how to interpret molecular pathogen assays and how to apply them to use fewer antibiotics instead of more.

Host response: molecular assays

Several interventions targeting the dysregulated host response were tested over the past decades without positive results, resulting in new drugs coming to the market [3]. The host response in sepsis is affected in a time-dependent matter, with studies suggesting a pro-inflammatory initial response and an immune-compromised second phase. It has been hypothesized that timing was an important issue in studies investigating immune-modulatory drugs [4]. More recently, transcriptomic analysis of blood leukocytes has yielded another possibility; there are between two and four different types of host responses in the initial phase of sepsis [5, 6]. A specific intervention can target only one such group and may harm the others, de facto resulting in insignificant or negative results.

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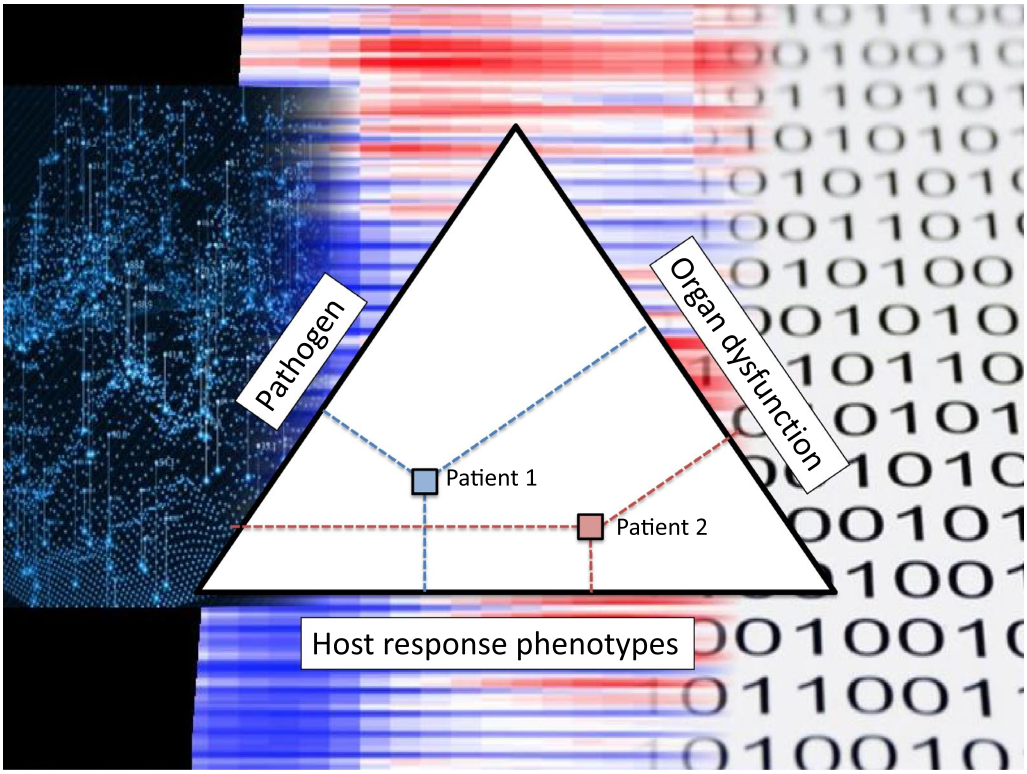

Fig. 1 Integrative approach to potential patient's trajectories based on the host, pathogen and organ dysfunction during Intensive Care Unit (ICU) admission

In a landmark study, Scicluna et al. described the transcriptomic landscape in a well-defined sepsis population. Importantly, they validated their findings in three separate cohorts [6]. They measured blood leukocyte expression profiles, something that, in theory, could be done in hours. Four biological phenotypes were identified with very distinct characteristics. Mortality was highest in the Mars1 phenotype, but those patients also more frequently had septic shock. However, the presence of shock did not explain the differences in mortality between phenotypes, as the Mars2 phenotype had similar shock rates, but a lower mortality. Gene expression showed a decrease in expression of genes involved in the innate and adaptive immune response. Just eight genes were sufficient to discriminate between the phenotypes with excellent accuracy. These results indicate that it does not make any biological sense to suppress immune response in all patients, which is now supported by a post hoc analysis of a randomized controlled trial [7]. Furthermore, a select group of patients may benefit from activation or restoration of a pro-inflammatory response [8].

Organ dysfunction: the challenge of big data

Electronic health records are becoming increasingly important for identifying and preventing organ dysfunction, but may lead to an information overload for the human mind. Data are not always presented in the most intelligent fashion and physicians may suffer from alert fatigue due to long work hours and too many false-positive alarms. In fact, we already have access to much more information than we can process in our current clinical practice [9]. Challenges for the coming years include: uniform data entry to allow for automated analysis of data, identification of the most important variables, shorter feedback loops between data entry and automated alerts and continuous improvement of alerts through artificial intelligence algorithms [10]. Combinations of organ dysfunctions seem to cluster and are related to mortality [11]. This is an excellent example of how the large epidemiological datasets can identify patterns of patient behavior that are difficult to dissect for (inexperienced) clinicians (Fig. 1).

The future is about integration of big data

In the ICU of the future, the concepts that we envision above are brought into practice. Broad-spectrum antibiotics are reserved for the first couple of hours of admission. After that, the pathogen is identified, in most cases through a molecular assay, and antibiotics can be targeted towards this pathogen. Host response is classified into biological phenotypes, and immune-modulatory drugs are administrated based on that information. Organ dysfunction is identified in an early stage, and by timely treatment of the underlying mechanisms, worsening is prevented. The ICU we describe lies in a distant future, but we can get closer one step at a time by working together in larger consortia, integrating big datasets covering molecular analyses to clinical characteristics. New trial designs, such as adaptive designs, need to be tested to allow for more flexible randomization than in a traditional randomized controlled trial. This is a challenge that cannot be taken by single individuals or single groups, and instead requires a group effort from the whole community with help from experts in molecular medicine, artificial intelligence and commercial management.

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