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What can we learn from elegant clinical studies?

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Sepsis is a major health problem in the United States with an increasing incidence of cases that surpass 750,000 per year and a mortality rate of approximately 20–50%. The health care costs associated with the treatment of septic patients is on a skyrocketing trajectory, which is estimated to be over \$16 billion per year (1, 2). To this day, the best therapy for sepsis is only supportive. Even after aggressive antibiotic treatment, some patients progress toward the development of severe sepsis, septic shock and organ failure, which has a mortality rate proportional to the number of organs that fail (3, 4). Currently, there are no reliable predictors for the incidence and progression of sepsis-related conditions, which makes accurate diagnosis and patient management more difficult. The development of septic shock is dependent upon the patient's own response to injury, which can involve a prolonged inflammatory response, resulting in the progression to immune dysfunction, or anergy, preceding death (5). Although the clinical and biological information regarding sepsis has been gathered from extensive clinical and experimental studies, the precise mechanisms involved in the progression from an initial insult to multiple organ failure are still very unclear. Therefore, more investigations regarding the development of sepsis in human and animal models could eventually clarify the view toward a sound therapy to ameliorate this detrimental condition. In this issue of *Critical Care Medicine*, Gomez, et al. (6) present a very extensive and elegant study of a large cohort of septic patients, which was focused on changes in the immune response during the period of hospitalization. The study has several important strengths, including the large number of subjects (148 patients) of similar ages (52 to 76 years old), a study period of more than a year to include any seasonal variability with appropriate weight of both sexes, and sustainable homogeneity in the ethnicity (92% Hispanic). Thus, the majority of confounding factors that modulate the response of sepsis were included (7). The report pointed out several important lessons.

The bulk of immunological parameters that were measured were elevated at the time of admission or enrollment with a slight, continuous decrease during the time of hospital stay (28 days). This information echoes early predictions that the immunological response is maximal at the earliest time points after the insult, followed by a decline, even if the disease is not fully controlled. This massive initial inflammatory response followed by a steady decrease of the process has been described as the landmark of the progression toward anergy as previously proposed (4, 6). In addition, the observation that the maximal immunological response is very close to the time of the insult, resembles the concept of the “Golden Hour” that has haunted the trauma community for decades. Although the “Golden Hour” rule has been mainly used for the early management of trauma patients, its application to other

conditions, such as sepsis, may be pertinent and, perhaps, should be rephrased as “the Golden Hours.” There is extensive literature both in favor and against this concept (8). However, it may be proven one day that early therapy is the best therapy. Indeed, clinical studies have shown that early therapy has increased survival from injury (9). Moreover, a study using an experimental mouse model of sepsis induced by cecum ligation and puncture has shown that the therapeutic window occurs very early, within 6 hours, of the initial insult (10). Although there is currently tremendous discussion as to whether or not animal studies could be useful in the understanding of the etiology of sepsis (11, 12), there is no doubt that much can be learned about sepsis from these little rodents. However, a mouse is not a human, but all humans are not all identical either.

Another lesson from the study of Gomez, et al. (6) is that there are immunological differences between survival and non-survival septic patients. Among them, interleukin (IL)-6 was shown to be increased in non-survival patients as opposed to survival patients, which was predicted again by experimental mouse models (13) and supported by other clinical studies (14, 15). However, caution should be exercised when interpreting the potential importance of the inverse correlation between elevated IL-6 levels and survival. The causes for the elevated levels of IL-6 are not completely understood and may be unrelated to its biological activity. Therefore, attempts to block IL-6 in septic patients may be, once again, destined to fail as many other single-bullet approaches have in the past. First, high levels of IL-6 may be related to the lack of the cytokine's clearance rather than massive production. In addition, the high levels of IL-6 may be part of the stage of innate immune dysfunction, or anergy, in which immune cells are non-responsive to the cytokine activity. Finally, the detection of high circulating levels of IL-6 may be well past the therapeutic window.

The closing lesson from the study of Gomez, et al. (6) is that both pro- and anti-inflammatory responses were observed simultaneously, disputing the argument that the inflammatory response comes in waves, with a pro-inflammatory response preceding the anti-inflammatory response. During evolution, the immune system probably evolved to activate both activities at the same time to assure that the pro-inflammatory response is attenuated in a timely manner to avoid secondary detrimental consequences. However, both activities, which may be simultaneous at the transcriptional level, may be different at the biochemical/biophysical levels by displaying various decay kinetics, different affinity constants for receptors, and an interaction with co-factors. Thus, although both are synthesized at the same time, their biological activities may be different, and prediction exclusively based on the transcriptome may not be completely translated to the functional level.

Although the study of Gomez, et al. (6) has many merits, it also has a few limitations, most of them related to the use of human subjects. Although patients may go through a routine clinical protocol at the time of hospital arrival, there are likely variations in treatment due to differences in professional expertise, approaches, and experiences. Similarly, patients are likely to become septic from different initial conditions, which may be extremely important in the development of the disease. Human studies are also limited by the number of samples that can be obtained. Thus, a blood sample every 24 h may miss some of the rapid changes in the inflammatory process during injury. This situation is particularly true for cytokines, which display a variety of clearance rates. For example, TNF- α has an apparently very short half-life in circulation. In addition, the information obtained from a blood sample is very limited and perhaps says little about the whole pathophysiology of the patients in which multiple organ systems are coordinating activities to combat injury and infection. Moreover, circulating monocytes may not necessarily reflect the complete contribution of the immune system to injury resolution. These limitations make any potential predictions difficult with

any clinical study. Therefore, the study of Gomez, et al. (6) needs to be taken with caution, although the elegance, quality, and relevance of the study are very significant. In summary, the study of Gomez, et al. (6) brings more important information to the clinical setting in our quest to understand and find interventions to the detrimental consequences of sepsis in our population.

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