Editorial

Does immunosuppression affect the course of septic shock?

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Although sepsis was recognized first by Hippocrates (c.a. 460–370 BC) more than 2,000 years ago, many components of this complex clinical picture yet await to be established due to the unmet need to overcome its untoward consequences such as mortality, morbidity and increased health care use costs (1). Today, excluding the data from the cardiac intensive care units, sepsis is the major reason for mortality at intensive care units (ICU), with sepsis and septic shock accounting for approximately 30–50% of ICU-related deaths (2,3).

The significance and complexity of this clinical phenomenon, as well as its adverse consequences, led the researchers and clinicians to perform several attempts to bring a better understanding of this disease, resulting in several varying definitions over the years. However, after the first description of the disease by Hippocrates, relating sepsis to blood putrefaction (septicemia) and fever, it took a remarkably long period to establish the association of the disease with microorganisms by the French chemist Louis Pasteur [1822–1895] (1). Recent significant progress in the definition of the disease terms of sepsis and its associated terms was introduced by a task force reviewing the issue in 2016. These recently introduced definitions can be summarized in the following three main points. The first one is the omission of the term "Severe Sepsis." Secondly, while a simple inflammatory response without organ dysfunction formerly could be defined as "sepsis," currently it is recognized as a simple "infection." Third, the current definition of sepsis requires the evidence of organ dysfunction accompanying the infection with a Sequential Organ Failure Assessment (SOFA) score higher than 2. In addition to these definitions, it is worthwhile to refer to the description of the "Septic Shock" as well, which is the clinical picture manifesting itself with infection and additional hypotension as measured by a mean arterial pressure (MAP) over 65 mmHg or a systolic blood pressure lower than 90 mmHg. Furthermore, the patient must be receiving vasopressor medication(s) and must have a lactate level higher than 2 mmol/L (4).

Besides the need for more precise descriptions to establish the clarifications within the disease complexity, several predictors of the disease await clarifications as well. Because, despite the efforts to prevent the untoward consequences of the disease by the innovative procedures in the diagnosis and management, the number of reported cases diagnosed with sepsis keep increasing worldwide annually. One reason for this may be the progressively increasing awareness about sepsis. Other reasons include natural as well as induced factors such as the increased proportion of older individuals in the population and chronic disorders on one hand and antibiotic resistance, invasive interventions like increasing use of immunosuppressive drugs and chemotherapies, and organ transplantations on the other.

Although the current hospital and intensive care unit practices may provide an advanced spectrum of measures with antibiotics treatments, fluid-electrolyte resuscitations, hemodynamic interventions, and mechanical ventilation in attempts to improve the adverse components of the prognosis of sepsis and septic shock, several other factors associated with the host and the pathogens determine the

course of the disease as well presenting other complexities. Predominantly, the host responses to the treatment manifest variations and heterogeneity even though the identical treatments are given to the patients with identical diagnoses. This heterogeneity is related to pathogens' virulence and to some demographic and genetic factors associated with the host. Some of these factors, including the age, gender, innate and adaptive immunity, comorbidities (including chronic diseases, malignant and nonmalignant immunosuppression), and site of infection, contribute to the development of the risk factors and impact on the prognosis of sepsis (5). Besides these host factors, each individual pathogen bears varieties in terms of virulence, invasiveness, and development of antibiotic resistance, eventually determining the development and severity of infections. However, similar to these genetic variabilities in a given pathogen, the innate heritable variations in the individuals strongly determine the risk of developing infections and its prognosis, too.

Malignancies (solid or hematologic), transplantations (solid organ or hematopoietic stem cell) and immunosuppression (acquired or congenital) impairing the innate and adaptive immunity appear to be the most significant risk factors for sepsis and septic shock. Many studies in the literature show that immunosuppression increases the incidence of sepsis and the mortality associated with sepsis. In particular, studies by Azoulay *et al.*, Pène *et al.*, and Soares *et al.*, have determined the prognosis and prognostic factors in cancer patients treated at ICU (6-8).

Similarly, the article by Jamme and colleagues has recently confirmed this reality (9). Jamme *et al.* examined 801 patients with sepsis in a period of 8 years retrospectively. Among these patients, 305 (38%) were immunocompromised in association with several factors including solid tumors, hematologic malignancies, and they were diagnosed with other non-malignant conditions, too. Aiming to compare the immunocompromised patients to their immunocompetent counterparts admitted to the ICU for the septic shock according to the type of the disease, causing immunosuppression, or according to the type of treatment in order to describe the prognostic characteristics during septic shock. Secondly, this comparison was made to determine the impact of each immunodeficiency profile on the short-term prognosis. As the analysis was confined only to evaluating the parameters of septic shock patients at the ICU, the impact of ICU-acquired sepsis on prognosis was not assessed. Another aim of the study was to demonstrate whether the immunocompromised patients with sepsis actually developed more infectious or non-infectious (ischemic or hemorrhagic) complications compared to the nonimmunocompromised patients. Finally, the study reported the two primary outcomes below:

(I) The all-cause immunosuppression was associated with an increased mortality rate. The patients with solid tumors exhibited higher mortality rates as compared to the other immunocompromised and nonimmunocompromised patients. An increased in-hospital mortality rate [cause-specific hazard, 2.20 (95% CI, 1.64–2.96); P<0.001] was observed in patients with solid tumors. In a multivariate analysis, the study demonstrated that the all-cause immunosuppression, solid tumors, and leukopenia were the independent predictors associated with the in-hospital mortality.

(II) The incidence of ICU-acquired infections was not different between the subgroups of immunocompromised and nonimmunocompromised patients. Leukopenia at admission was not associated with an increased risk of ICU-acquired infections, either. In contrast, severe bleeding events were more likely in patients with hematologic malignancies [cause-specific hazard, 3.17 (95% CI, 1.41–7.13); P=0.005). In addition, the ischemic complications were more likely in those patients with nonmalignant immunosuppression [cause-specific hazard, 2.12 (95% CI, 1.14–3.96); P=0.02).

Because most of these studies in the literature bear several limitations in determining the significance of immunodeficiency in ICU infections, this current study has been added to the literature as a supporting article showing the impact of the immune status on the prognosis of septic shock and ICU-acquired complications. The limitations of the previous studies include the failure to detail the underlying causes of immunodeficiency, the lack of individual evaluation of the underlying factors, focusing only on one of the immunodeficiency profiles, such as AIDS or malignancies, or only on one type of infection such as bloodstream infections or pneumonia. However, the study by Jamme *et al.* assessed the impact of various immunosuppressive factors on the septic shock prognosis. In addition, originality of this current study presented above is the assessment of important endpoints including mortality as well as the development of both infectious and noninfectious complications in clinically relevant subgroups of patients.

At this point, it might be notable to include the study

of Tolsma *et al.* (10) in the literature as another study on this issue, evaluating the influence of the immune profiles on septic shock or severe sepsis prognosis in patients treated at ICU on day 28. The study defined seven profiles of immunodeficiency, all of which were associated with an increased risk of mortality during short-term ICU admissions.

However, the study by Jamme *et al.* has several limitations. First, it is a single center study. Secondly, the retrospective design may have influenced the quality of the data collection and results. Third, a number of patients had been subjected to end of life decisions and therefore underwent limited diagnostic and therapeutic procedures. Fourth, they did not evaluate the clinical outcomes such as hospital-acquired complications, or residual organ dysfunctions in the period following the discharge from the ICU. However, it is still a valuable, original and one of the few studies showing the prognosis of septic shock in immunocompromised patients, whose immunosuppression was associated with various causes.

In conclusion, immunosuppression due to various causes is currently common worldwide. Furthermore, in patients with sepsis/septic shock, it is demonstrated that immunodeficiencies are common. The underlying immunodeficiency impacts on the course of sepsis/septic shock. Further studies are required to determine the characteristics of sepsis and septic shock more precisely according to the individual immunodeficiency profiles of patients.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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References

1. Funk DJ, Parrillo JE, Kumar A. Sepsis and septic shock: a history. Crit Care Clin 2009;25:83-101, viii.
2. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34:344-53.
3. Pavon A, Binquet C, Kara F, et al. EPIdemiology of Septic Shock (EPISS) Study Group. Profile of the risk of death after septic shock in the present era: an epidemiologic study. Crit Care Med 2013;41:2600-9.
4. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801-10.
5. Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA 2014;311:1308-16.
6. Azoulay E, Mokart D, Pène F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en réanimation onco-hématologique study. J Clin Oncol 2013;31:2810-8.
7. Pène F, Percheron S, Lemiale V, et al. Temporal changes in management and outcome of septic shock in patients with malignancies in the intensive care unit. Crit Care Med 2008;36:690-6.
8. Soares M, Caruso P, Silva E, et al. Characteristics and outcomes of patients with cancer requiring admission to intensive care units: a prospective multicenter study. Crit Care Med 2010;38:9-15.
9. Jamme M, Daviaud F, Charpentier J, et al. Time course of septic shock in immunocompromised and nonimmunocompromised patients. Crit Care Med 2017;45:2031-9.
10. Tolsma V, Schwebel C, Azoulay E, et al. Sepsis severe or septic shock: outcome according to immune status and immunodeficiency profile. Chest 2014;146:1205-13.

