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Victims or culprits, B-cells may serve as markers for mortality risk and targeted therapy in sepsis

Zoltán Spolarics, M.D, Ph.D.

Department of Surgery, Rutgers-New Jersey Medical School, Newark, NJ

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In this issue of Critical Care Medicine, Shankar-Hari and colleagues report novel and original observations supporting the notion that B-cell dysfunction is a contributing player in sepsis-associated immune disturbance. Furthermore, markers of B-cell function could identify a subgroup of patients with increased mortality risk and candidacy for effective immunoglobulin therapy [1].

Immune dysfunction in sepsis is a complex phenomenon and impacts all major cell types of innate as well as adaptive immunity. Among the multiple biological markers associated with sepsis, one of the hallmarks of cellular changes is the depletion and dysfunction of circulating as well as tissue-resident lymphocytes including T and B-cells [2, 3]. Most of the lymphocyte studies in the context of sepsis focused on T-cells because the well-known connections between the adaptive and innate immunity through cross talking among T-cells, macrophages, dendritic cells and polymorphonuclear phagocytes. Now, it is well established that a more severe T-cell depletion or dysfunction is associated with increased clinical complications and mortality risk [4, 5]. Even though B lymphocytes are also depleted in sepsis [5], B-cell dysfunction has been less investigated because the connection between B-cell activation and differentiation and the innate immune response to sepsis is less evident. However, after animal studies revealed multiple connections between B-cell responses and the early innate response, clinical studies started to test sepsis-induced B-cell alterations and the association between B-cell dysfunction and mortality risk [5–7]. It was also found that patients who survived a severe septic episode may display immune dysfunction and increased susceptibility to infections long after recovering from the initial septic insult which could in part be associated with continuing post-septic B-cell dysfunction [8, 9]. Thus, depressed B-cell function could impact sepsis by interaction with the innate immune response as well as by compromising adaptive immunity.

Upon interactions with antigens, B-cells differentiate into antibody producing plasma cells. Antibodies are composed of two heavy chains and two light chains. Structural variations in heavy chains give rise to the five major classes of immunoglobulins (IgG, IgM, IgD, IgA and

IgE). Any given immunoglobulin has either two light chains kappa or two light chains lambda, never one of each under normal conditions [10, 11]. The heavy and light chains of immunoglobulins are produced and assembled in B-cells and plasma cells. Under normal conditions, more light chains than heavy chains are produced within cells and the excess in light chains is released and appears in blood. Sepsis-induced disturbances in immunoglobulin production and assembly are supported by observations indicating decreased immunoglobulin concentrations in septic patients. Unexpectedly, decreased blood immunoglobulin levels alone did not identify increased mortality risk in previous studies [12]. It was also shown that circulating concentrations of free kappa and lambda light chains are elevated in sepsis or conditions predisposing to sepsis [13, 14].

These observations, together with the sepsis-induced B-cell depletion, indicate major disturbances in antibody production and assembly and served as the basis for the authors' hypothesis that concomitantly reduced immunoglobulin and increased light chain blood levels could serve as markers of increased mortality risk and could also identify a subgroup of patients with candidacy to intravenous immunoglobulin therapy. The proposed approach is original and valuable. The paper demonstrates that when the mean value of free light chains or immunoglobulins concentration is compared between sepsis survivors and non-survivors this comparison does not reveal increased mortality risk in accordance with previous observations. However, when patients are stratified by grouping according to normal or abnormal levels of light chain concentrations and the concomitant accompanying levels of normal or abnormal immunoglobulin concentrations, the mortality risk is readily manifested. Using this analytical approach, the authors demonstrate that abnormally high levels of light chain lambda is accompanied by increased mortality risk independent of whether the accompanying IgG or IgM levels are in the normal or abnormally range. They also show that the association between abnormal free light chain lambda concentration and increased risk of sepsis mortality is independent of illness severity.

It is important to mention that the authors used normal reference ranges of adult general population to set the normal and abnormal levels of free light chain and immunoglobulin blood concentrations. This is important because the normal concentration range of these proteins is rather wide in healthy adults (2.6–6.3-fold range) and likewise expected to be variable in septic patient. The great variability in immunoglobulin and free light chain blood content may blunt or mask potential individual differences within the cohort when mean blood concentrations between survivors and non-survivors are compared. However, stratifying by abnormal levels using normal reference ranges could identify specific subgroups within the cohort revealing differences in mortality risk or other clinical markers just like the authors did successfully in this study. Another advantage of using accepted reference range values is that follow-up studies could use the same stratification criteria which would make comparisons among independent studies easier and more reliable.

An additional interesting observation of the study is the appearance of circulating B-cells with a dual membrane expressions of light chains kappa and lambda in septic patients. As mentioned before, mature B-cells produce only a single class of immunoglobulin heavy chain and a single class of light chain, either kappa or lambda. This paradigm is called the one B cell-one antibody rule. The mono-specificity of B cells is achieved by the allelic

exclusion of heavy and light chain genes [10]. Simultaneous expression of these molecules is restricted to malignancies or de novo somatic mutations [11]. Dual chain expressing B-cells are less specific in binding to antigens and may also cause collateral damage through non-specific interactions. Thus, the appearance of kappa-lambda dual positive B-cells in sepsis demonstrated in the study is remarkable and suggests severe disturbances in the regulation of gene expression and allelic exclusion. The fact that the increased number of dual positive B-cells positively correlated with free light chain lambda and kappa blood levels suggests their possible role in causing the changes. It remains to be seen whether the appearance of dual positive B-cell is reversible and disappear upon recovering from sepsis. The caveat of this observation however is that this component of the studies was done in a sub-group of 21 patients and the cohort presented only one death. Thus, the potential association between mortality risk and the presence of double positive B-cells and associated changes in light chain blood content could not be tested.

Taken together, the study is an important contribution to previous observations confirming that even a severe drop in blood immunoglobulins alone is not a reliable predictor of sepsis mortality. Immunoglobulin and B-cell dysfunction status should be interpreted by the accompanying levels of free light chain concentrations. The study also supports the notion that B-cell dysfunction is an important contributor to sepsis-associated immune dysregulation and mortality. The question however that B-cells are victims or culprits of immune dysfunction remains unanswered. B cell depletion is presents at the early phase of sepsis or could also manifest soon after injury or burns suggesting prompt activation and apoptosis of B-cells in response to the cytokine storm and signals from injured tissues and activated cells. B-cell depletion and dysfunction with the accompanying decrease in immunoglobulin production could affect a variety of innate immune functions including opsonization and clearance of pathogens. Increased concentration of free circulating light chains may compete or interfere with antigen-antibody or antigen-cell interactions affecting immune reactions as well as antibody production. Based on these facts, it seems almost irrelevant to contemplate whether B-cells are causative culprits or innocent victims in the septic cascade because, independent of the mechanism, a severe depletion and dysfunction of this key cellular element of the adaptive immune response must impact sepsis recovery or post-sepsis susceptibility to infections.

The etiology of sepsis is complex. Cellular and organ responses may grossly vary among individuals; and septic cohorts contain heterogeneous populations concerning age, sex, racial and ethnic backgrounds, genetic polymorphisms, underlying disease, and medical history. These facts clearly indicate that there is a need to identify reliable biomarkers, which can sub-stratify patients according to immune phenotypes or increased mortality risks. A reliable set of markers could enable physicians to employ targeted therapeutic interventions for septic subgroups identified by set criteria. Using B-cell markers in a fine-tuned analytical approach, like that presented by Shankar-Hari and colleagues in this paper, is an appreciable effort in this context and could become a useful tool in identifying high-risk individuals within a cohort eligible for targeted therapy. Whereas the proposed concept is important, relevant and timely, characterization of extreme septic clinical phenotypes is still at its rudimentary stage and therefore, as stated by the authors, “warrants further studies”.

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