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Early natural killer cell counts in blood predict mortality in severe sepsis

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Abstract

Introduction: Host immunity should play a principal role in determining both the outcome and recovery of patients with sepsis that originated from a microbial infection. Quantification of the levels of key elements of the immune response could have a prognostic value in this disease.

Methods: In an attempt to evaluate the quantitative changes in the status of immunocompetence in severe sepsis over time and its potential influence on clinical outcome, we monitored the evolution of immunoglobulins (IgG, IgA and IgM), complement factors (C3 and C4) and lymphocyte subsets (CD4+ T cells, CD8+ T cells, B cells (CD19+) and natural killer (NK) cells (CD3-CD16+CD56+)) in the blood of 50 patients with severe sepsis or septic shock at day 1, day 3 and day 10 following admission to the ICU.

Results: Twenty-one patients died, ten of whom died within the 72 hours following admission to the ICU. The most frequent cause of death ($n = 12$) was multiorgan dysfunction syndrome. At day 1, survivors showed significantly higher levels of IgG and C4 than those who ultimately died. On the contrary, NK cell levels were significantly higher in the patients who died. Survivors exhibited a progressive increase from day 1 to day 10 on most of the immunological parameters evaluated (IgG, IgA, IgM, C3, CD4+, CD8+ T cells and NK cells). Multivariate Cox regression analysis, including age, sex, APACHE II score, severe sepsis or septic shock status and each one of the immunological parameters showed that NK cell counts at day 1 were independently associated with increased risk of death at 28 days (hazard ratio = 3.34, 95% CI = 1.29 to 8.64; $P = 0.013$). Analysis of survival curves provided evidence that levels of NK cells at day 1 (> 83 cells/mm³) were associated with early mortality.

Conclusions: Our results demonstrate the prognostic role of NK cells in severe sepsis and provide evidence for a direct association of early counts of these cells in blood with mortality.

Introduction

Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed by fluid resuscitation) are major healthcare problems that affect millions of individuals around the world each year, killing one in four (and often more) and increasing in incidence [1-3]. Similarly to polytrauma, acute myocardial infarction and stroke, the early initiation of therapy once severe sepsis is established is likely to influence the patient's prognosis. In

consequence, early identification of individuals at risk for bad outcomes is dramatically important in this condition [4].

Because sepsis originates from a microbial infection, host immunity should play a principal role in determining both outcome and recovery. A protective role of naturally produced immunoglobulin G (IgG) in sepsis was described previously [5]. The participation of cellular immunity in this disease is poorly understood, and the available data are controversial [6-8].

Identifying quantitative alterations in key humoral and cellular parameters could have a prognostic value in this condition. In an attempt to evaluate the quantitative changes in the status of immunocompetence in severe

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