

LETTER

The predictive role of early activation of natural killer cells in septic shock

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See related research by Andaluz-Ojeda *et al.*, <http://ccforum.com/content/15/5/R243>, and related research by Monserrat *et al.*, <http://ccforum.com/content/13/1/R26>

Abstract

Recently, several studies about the role of natural killer (NK) cells in sepsis have been highlighted. In an earlier study, we characterized the abnormalities of circulating lymphocytes in 52 patients with septic shock during the first 28 days in the intensive care unit. Our results confirm and expand some previous reports. We found that patients who did not survive exhibited less NK cell (CD3⁻CD56⁺) depletion than survivors and that these NK cells expressed CD69⁺ and CD57⁺. These data demonstrate that NK cells are key participants in septic shock because patients who survived have more depletion and expressed less early activation and differentiation.

In a study that was published in a recent issue of *Critical Care* and that was conducted in a cohort of 50 patients with severe sepsis at intensive care unit (ICU) admission, Andaluz-Ojeda and colleagues [1] reported that absolute counts and relative concentrations of natural killer (NK) cells were significantly higher in patients who died.

In an earlier study, also published in *Critical Care*, we characterized the abnormalities of lymphocytes in 52 patients with septic shock during the first 28 days in the ICU [2]. Thirty-six healthy subjects served as controls. The study design was approved by the university hospital ethics committee, and all participants or their next of kin provided written informed consent.

Table 1 shows the significant differences found in the counts and percentages of lymphocyte subpopulations during the first week of follow-up. Like previous investigators,

we have found a reduced count of circulating NK cells in patients with septic shock, independently of their outcome [1,3]. Although patients who did not survive exhibited less NK cell depletion than survivors at ICU admission, there were no differences in CD56⁺CD3⁻ cell counts in blood between survivors and non-survivors. These data are slightly in agreement with those reported by Andaluz-Ojeda and colleagues [1], who found that patients with the highest NK cell number had the lowest probability to survive. However, unlike Giamarellos-Bourboulis and colleagues [4], we did not find higher percentages of NK cells in patients who did not survive.

Using CD69 and CD57 surface antigens, we determined the counts and distributions of the activation stage of NK cells (CD3⁻CD56⁺) by flow cytometry. We obtained a significant increase in the counts and percentages of the CD3⁻CD56⁺CD69⁺ cells in non-survivors at ICU admission and on day 3 (Figure 1). The mean fluorescence intensity for CD56⁺CD3⁻CD69⁺ cells was also significantly higher in non-survival patients than in survivors or controls (30.6 ± 4.2 versus 20.3 ± 2.6 and 18.3 ± 0.9, respectively; *P* < 0.05 for both). CD69 is rapidly induced in NK cells after activation and its role in NK cytotoxicity has been demonstrated in humans [5].

We further found a significantly higher percentage of CD3⁻CD56⁺CD57⁺ NK cells in non-survival patients than in survivors and controls at ICU admission (70.8% ± 3.3% versus 57.3% ± 9.2% and 53.6% ± 3.7%, respectively; *P* < 0.05). Non-survivors had a strong but not significant trend toward an increase of CD3⁻CD56⁺CD57⁺ NK cell count (94.8 ± 7.3 versus 56.9 ± 12.4 cells per cubic millimeter). The expression of CD57, a long-lived marker and highly differentiated effector of NK cells, is increased in septic shock patients who died.

These data demonstrate an important role of NK cells as key participants in the early inflammatory response during septic shock. Patients who did not survive exhibited less NK cell depletion than survivors and these cells were very early activated and rapidly differentiated. We propose to assess NK cell phenotype and functions for

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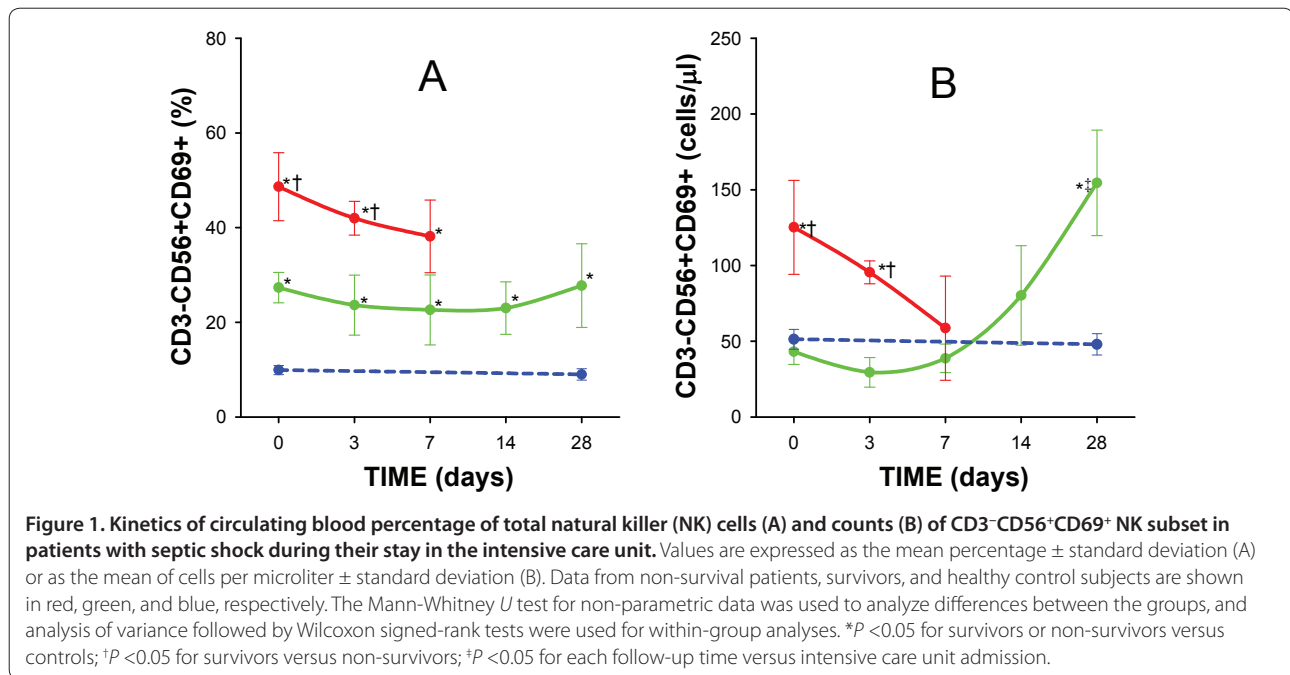
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Table 1. Counts and percentages of lymphocytes and their main subpopulations during the first week of follow-up in patients with septic shock and in healthy controls

		At ICU admission		After 48 hours		On 7th day		
		Healthy controls	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors	Survivors
Lymphocytes	Count	2,095.9 ± 67.0	1,235.3 ± 178.9 ^a	1,048.4 ± 192.0 ^a	1,235.3 ± 178.9 ^a	1,048.4 ± 192.0 ^a	863.3 ± 36.6 ^a	886.2 ± 178.9 ^a
	Percentage	30.4 ± 2.0	7.0 ± 1.7 ^a	4.6 ± 0.7 ^a	9.5 ± 0.4 ^{ab}	5.0 ± 1.1 ^a	4.4 ± 0.9 ^a	5.8 ± 0.9 ^a
CD3 ⁺	Count	1,393.6 ± 36.1	745.9 ± 145.7 ^a	740.0 ± 151.8	800.1 ± 10.2 ^a	558.9 ± 170.1 ^a	712.8 ± 69.7 ^a	574.9 ± 147.6 ^a
	Percentage	71.4 ± 1.7	59.9 ± 6.1	65.9 ± 4.2	70.0 ± 0.8	56.7 ± 8.9	73.1 ± 5.9	63.8 ± 4.6
CD19 ⁺	Count	238.5 ± 13.2	259.8 ± 83.8	162.8 ± 36.3	170.2 ± 4.0	199.3 ± 64.2	131.7 ± 83.9	112.2 ± 23.4 ^a
	Percentage	10.7 ± 0.9	21.8 ± 6.9	15.9 ± 3.0	16.2 ± 0.63 ^a	18.7 ± 2.2 ^a	14.2 ± 9.5	14.3 ± 2.3
CD56 ⁺ CD3 ⁻	Count	356.8 ± 28.4	191.8 ± 46.8 ^a	127.7 ± 30.3 ^a	125.3 ± 4.0 ^a	120.1 ± 53.3 ^a	83.8 ± 47.0 ^a	116.6 ± 36.6 ^a
	Percentage	16.8 ± 1.9	16.1 ± 3.3	18.6 ± 2.9	14.0 ± 0.82	12.5 ± 3.7	7.9 ± 3.9	13.2 ± 2.2

All values are expressed as mean ± standard deviation. 'Count' values are presented as cells per cubic millimeter, and 'Percentage' values are presented as percentages. The Mann-Whitney *U* test for non-parametric data was used to analyze differences between the groups. ^a*P* < 0.05 between septic shock patients and healthy controls. ^b*P* < 0.05 between survival and non-survival patients with septic shock. ICU, intensive care unit.



a better understanding of the physiopathology of sepsis in order to apply new therapies at an early stage.

Abbreviations

ICU, intensive care unit; NK, natural killer.

Competing interests

The authors declare that they have no competing interests.

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