Eosinophilia: An early marker of adrenal insufficiency in critically ill patients with septic shock?

Mouloudi E[1] MD, PhD, Katsanoulas K[2] MD, PhD, Aslanidis Th[3] MD, Lampiri Cl[4], MD, Papageorgiou Ch[5] MD, Tholioti Th[1] MD, Vrochides D[6] MD, PhD.

ABSTRACT

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Adequate adrenocortical function is essential to survive critical illness. The goal of this study was to determine whether eosinophilia could serve as a useful and early marker of adrenal insufficiency in critically ill patients with severe septic shock. During a 1-year period, we prospectively studied 294 ICU patients.16 patients (5.4% of ICU admissions) with eosinophilia more than 3% of the white blood cell count and septic shock unresponsive to adequate fluid and vasopressor therapy, were included. A high dose (250 mcg i.v) corticotropin stimulation test was performed. Eosinophilia (>3%) was diagnosed in 16 patients with vasopressor-unresponsive septic shock. Eosinophilia was present 1.9±0.9d (range 8-96h) before the onset of septic shock. 11/16 patients failed to respond to corticotropin stimulation test above the critical level of 9 mcg/dL rise and 2/16 had baseline cortisol concentration <10 mcg/dL. Baseline cortisol level, maximal cortisol increase post-corticotropin administration and Eosinophils count (%) were higher in survivors (p≤0.05). A hydrocortisone infusion (300mg/d) treatment resulted in haemodynamic improvement in 12 of 16 patients (75%). The 28-day mortality (following the onset of septic shock) was 43.7%. Relative eosinophilia may be considered as a useful and early bioassay for adrenocortical function assessment in critically ill patients with septic shock and assumed adrenocortical depression.

[1]Intensive Care Unit, "Hippokratio" General Hospital, Thessaloniki, Greece

[2]Anesthesia Department, "Hippokratio" General Hospital, Thessaloniki, Greece

[3]Mobile Intensive Care Unit, NCEC, Thessaloniki Department, Greece

[4]Intensive Care Unit, General Hospital of Kavala, Kavala, Greece

[5]Anesthesia Department, "Charles-Foix" Hospital, Paris, France

[6]Surgery, HPB and Transplant Department, Hippokratio" General Hospital, Thessaloniki, Greece

INTRODUCTION

The number of circulating Eos has been suggested as marker for adrenocortical function[1-3]. Corticosteroids exert eosinopenic effects, at least in part, by stimulating eosinophil apoptosis[4]. It has been suggested that the presence of relative eosinophilia (eosinophils counts higher than 3% of the WBC count) in critically ill patients is associated with clinical signs of adrenal insufficiency[1].

The role of steroids in the treatment of septic shock in critically ill patients with adrenal insufficiency has provoked significant interest. Intravenous corticosteroids (hydrocortisone 200-300mg/daily) are recommended by some studies in patients with septic shock unresponsive despite adequate fluid replacement and vasopressor therapy[4-6]. The use of a 250 mcg corticotropin stimulation test for identifying responders (as for more than 9mcg/dL maximal increase in serum level cortisol, 30-60 minutes post-corticotropin administration) in these patients is not considered optional, as the overall trial population appears to benefit from this treatment regardless of stimulation response.

The goal of this study was to determine whether eosinophilia could serve as a useful and early marker of adrenal insufficiency in critically ill patients with septic shock.

MATERIAL AND METHODS

After hospital's ethical committee approval, we studied prospectively all 294 adult patients admitted in an adult mixed ICU during one-year period. Inclusion criteria were Eosinophilia (Eos>3% of WBC) and septic shock unresponsive to fluid and vasopressor therapy. Patients receiving corticosteroids, those with history of adrenal insufficiency and those who had received etomidate[7,8], were excluded. None of the studied patients had an allergic reaction or a history of parasitic infection. Apart from that, patients were enrolled in the study if they had clinical evidence of infection, evidence of systemic inflammatory response (SIRS) and met the criteria for septic shock[9]. All included patients required infusion of 0,2 mcg/kg/min or more of norepinephrine and had at least two out of six major organ systems dysfunction (SOFA score of 3 or 4 points for each organ system)[10].

A high dose (tetracosactrin 250 mcg iv, Synacthen®) corticotropin stimulation test was performed in all included patients. Plasma cortisol levels were measured by radioimmunoassay at baseline and at intervals of 30 and 60 minutes after the corticotropin stimulation test. A baseline cortisol level <10 mcg/dL was considered suggestive of absolute adrenal insufficiency[11]. Maximal increase of serum cortisol ≤ 9mcg/dL 30-60 min post-corticotropin administration,

was considered suggestive of relative adrenal insufficiency[6, 11].

All studied patients were treated with low dose hydrocortisone (300 mg/day by continuous i.v. in-fusion). Haemodynamic response to the administration of corticosteroids (successful discon-tinuation of vasoactive agents within 48 hours after the start of corticosteroids) was also studied.

Severity of illness was assessed via APACHE II score on the day of ICU admission and SOFA score on the day of corticotropin stimulation test. Demographic data, diagnoses on admission, significant medical history, clinical and biological data at the onset of septic shock, inotropic support, infection data, duration of ICU stay, and ICU and 28-day mortality, were also collected.

Statistical analysis was performed with SPSS Statistics for Windows, v.17.0 (SPSS Inc®, Chicago Ill, USA). After normality test, analysis was carried out via Student's t-test and chi-square analysis. Due to small sample further multivariate analysis were not performed. Statistical significance was defined as $p<0.05$.

RESULTS

During the one-year study period, 294 patients were admitted to the ICU. Of these patients, sixteen (5.4% of ICU admissions) with eosinophilia more than 3% of the WBC count and vasopressor unresponsive septic shock, were included in the study. Two out of 16 patients (12.5%) had baseline cortisol concentration less than 10 mcg/dL and 11 out of 16 patients (68.7%) failed to respond to corticotropin stimulation test above the critical level of 9 mcg/dL. Demographic characteristics of the patients, admitted diagnoses, significant medical history are presented in Table 1.

Table 1. Demographic characteristics

Parameters	All patients N (%) N=16	Survivors N (%) N=9	Non-survivors N (%), N=7	p
Age (yrs)	**47.2±18.7**	**38.4±17**	**58.5±15**	**p≈0.02**
Sex (male)	**13 (81.2)**	**8 (88.8)**	**5 (71.4)**	**NS**
Significant Medical History				
Hypertension	**1 (6.2)**	**1 (11.1)**		**NA**
Coronary artery disease	**1 (6.2)**	**1 (11.1)**		**NA**
COPD†	**3 (18.7)**	**1 (11.1)**	**2 (28.5)**	**NS**
Admission Category				
Medical	**5 (31.2)**	**2 (22.2)**	**3 (42.8)**	**NS**
Surgical	**3 (18.7)**	**2 (22.2)**	**1 (14.2)**	**NS**
Trauma	8 (50)	5 (55.5)	3 (42.8)	NS

Plus minus values presented are mean ±SD, †: Chronic Obstructive Pulmonary Disease, NS: Non-significant NA: not applicable for analysis

Only age differ among survivors and nonsurvivors. Clinical and biological data at the onset of septic shock, APACHE II score on the day of admission to the ICU and SOFA score on the

day of cortico-tropin stimulation test, Eos counts, baseline cortisol level, cortisol level 30 and 60 minutes post-corticotropin administration, maximal cortisol increase post-corticotropin administration are presented in Table 2.

Table 2. Baseline patient's clinical and biological characteristics and adrenal response after cortico-tropin stimulation

Parameters	**All patients N (%) N=16**	**Survivors N (%) N=9**	**Non-survivors N (%), N=7**	**p**
Temp (^oC)	38.8±0.7	38.9±0.3	38.7±1	NS
HR (bpm)	121.6±10.7	122.6±11.1	120.3±11	NS
SBP (mmHg)	84.8±6.1	84.5±8.6	85.3±3.1	NS
CVP (mmHg)	12.1±2.3	12.1±2.4	12.1±2.5	NS
APACHE II score†	18.6±6.8	18±6.8	19.2±7.3	NS
SOFA score	10.3±2.7	9.6±2.7	11.3±2.7	NS
Leukocytes (thousands/ /mm^3)	10.5±3.9	11.1±4.9	9.8±2	NS
Platelets (thousands/ /mm^3)	238±183	261±225	207±121	NS
Arterial pH	7.36±0.07	7.37±0.08	7.36±0.08	NS
PaO_2/FiO_2‡	191±117.4	213.7±139.2	160±82.3	P≈0.05
Serum Cortisol				
Before corticotrophin	19.4±8.1	20.7±5.4	17.7±10.9	p<0.05
30 min after corticotropin	25.7±9.6	27.5±5.6	23.5±13.4	NS
60 min after corticotropin	27.2±9.7	29.4±5.9	24.3±13.1	NS
Maximum responseto corti-cotropin	8.35±4.9	8.9±5.7	7.4±3.9	p=0.05
Responders (>9mcg/dL re-sponse)	5 (31.2%)	3 (33.3%)	2 (28.5%)	P≈0.05
Eosinophil count (%)	6.9±3.5	7.3±3.4	6.4±3.9	P<0.05
Vasopressor: norepineph-rine infusion (mcg/kg/min)	0.3±0.007	0.29±0.008	0.32±0.06	NS

Plus-minus values are mean ±SD, temp:temperature, HR:Heart rate, SBP: Systolic Blood Pressure, CVP:Central Venous Pressure, †: on the day of admission to the ICU, ‡:Ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, NS: Non-significant

Baseline cortisol level, maximal cortisol increase post-corticotropin administration and Eos count (%) were higher in survivors ($p \leq 0.05$). Table 3 presents sites of infection and strains diagnosed at the onset of septic shock

Table 3. Sites of infection, strains diagnosed at the onset of septic shock and appropriate antimicrobial therapy.

Parameters	**All patients N (%), N=16**	**Survivors N (%), N=9**	**Non-survivors N (%), N=7**
SITES OF INFECTION			
Blood-stream	8 (47.1)	3 (30)	5 (71.4)
Lung	8 (47.1)	6 (60)	2 (28.5)
Abdominal	1 (5.8)	1 (10)	
MICRO-ORGANISMS			
Gram-negative	14 (73.7)	10 (83.3)	4 (57.9)
Gram-positive	3 (15.8)	1 (8.3)	2 (28.5)
Fungi	2 (10.5)	1 (8.3)	1 (14.3)
Appropriate therapy	13 (81.2)	8 (88.8)	5 (71.4)

A hydrocortisone infusion (300mg/day) treatment resulted in haemodynamic improvement in 12 of 16 patients (75%). Once treatment with hydrocortisone was initiated, eosinophilia resolved (ie, the Eos count was 0%) within 24 hours in all patients. Length of ICU stay was 34.4±23.1 days (43.5±23.9 days for survivors and 22.7±17 days for nonsurvivors). Among nonsurvivors 71.4% received at least 50% of the doses of hydrocortisone. Seven patients (43.7%) died within the 28-day period following the onset of septic shock and nine during their ICU stay (56.3%).

DISCUSSION

The number of circulating Eos has been proposed as an indicator of adrenocortical function 66 years ago[12]. It was observed that an increase in circulating Eos in critically ill patients was associated with clinical signs of adrenal insufficiency. Beishuizen et all.[1] conducted a prospective evaluation of 570 ICU patients. Relative eosinophilia was found in 40 of them and the low-dose corticotropin test showed insufficient response in 10 out of 40 patients. Eight out of 10 individuals with an abnormal corticotropin test had clinical signs of adrenal insufficiency and treatment with hydrocortisone resulted in haemodynamic improvement in seven of these eight patients. Angelis et all.[2] studied prospectively all 1022 surgical patients admitted to the surgical ICU with relative eosinophilia. Thirty-one of 70 patients with relative eosinophilia had adrenal insufficiency. Treatment with hydrocortisone resulted in haemodynamic improvement in 82% of the patients.

The cause of eosinophilia in adrenal insufficiency is not clear. The amount of circulating Eos in the peripheral blood depends on the production rate in the bone marrow, mean Eos survival time, and elimination time in circulating blood[13]. Corticosteroids modulate the expression of adhesion and migration factors, resulting in a higher transition rate of Eos out of circulating blood to the tissues. Eos also seems, to be an important additional source of macrophage migration factor, which could potentially have an inhibitory role in corticosteroids function[13]. Corticosteroids also exert eosinopenic effects, at least in part by stimulating eosinophil apoptosis[4].

Routine testing of adrenal function as corticotropin stimulation test had been advocated to guide corticosteroid therapy[6, 14-15.] A baseline cortisol level <10mcg/dL is suggestive of absolute adrenal insufficiency, while a maximal increase of serum cortisol ≤9mcg/dL 30-60 minutes post-corticotropin administration, is suggestive of relative adrenal insufficiency[6,15]. More than 50% of patients with septic shock had a blunted cortisol response[15]. The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock[5]. In 12 out of 16 patients (75%) with eosinophilia and unresponsive to adequate fluid and vasopressor therapy septic shock, had adrenal insufficiency. One of them, had absolute adrenal insufficiency, 11 out of 16 relative adrenal insufficiency and one had absolute and relative adrenal insufficiency. As relative eosinophilia (to over 3%) was present 1.9±0.9 days (range, 8 hours to 4 days) before the onset of septic shock, perhaps it may be consider as an early bioassay to estimate adrenocortical function.

None of the studied patients had a history of adrenal insufficiency or had received corticosteroids and/or etomidate. It is recognized now, that etomidate will suppress the hypothalamic-pituitary-adrenal axis and increases rate of death[7-9].

The use of corticosteroids as an adjunctive therapy in septic shock patients has been controversial for decades[6, 16-18]. Intravenous corticosteroids (hydrocortisone 200-300mg/daily) are suggested in patients with septic shock who despite adequate fluid replacement and vasopressor therapy were unable to restore hemodynamic stability[16]. CORTICUS study[16] enrolled septic shock patients requiring vasopressor administration, but without the criterion for ongoing hypotension. Annane studies[6] enrolled patients with septic shock and refractory hypotension despite fluid resuscitation and vasopressor administration. An analysis of patients in CORTICUS study[16] who had a systolic blood pressure that persisted below 90 mmHg at 1st day after fluid and vasopressor resuscitation showed an absolute reduction in mortality of 11.2% in the hydrocortisone group versus in placebo group (results that are simi-

lar to those reported by Annane et al[6]). In our study, we enrolled patients with relative eosinophilia and fluid and vasopressor unresponsive septic shock. Baseline cortisol level, maximal cortisol increase post-corticotropin administration and Eos count (%) were higher in survivors ($p \leq 0.05$). A hydrocortisone infusion (300mg/ /day) treatment resulted in haemodynamic improvement in 12 of 16 patients (75%).

Severe sepsis and septic shock are major causes of mortality and morbidity worldwide[5]. A death rate of 33 to 61% has been reported for severe sepsis and septic shock[6, 19-20]. Seven patients in our study (43.7%) died within the 28-day period following the onset of septic shock and two more during their ICU stay (56.3%). Among nonsurvivors 71.4% received at least 50% of the doses of hydrocortisone and 28.6% had received inappropriate antibiotic therapy, that may has influenced their outcome, as among survivors 88.8% had received appropriate antibiotic therapy.

Although the number of the included patients in our study is small and further studies should be carried out, we conclude that relative eosinophilia in critically ill patients with fluid and vasopressor unresponsive septic shock might be considered a useful and early marker of adrenal insufficiency and a guide for corticosteroid therapy[22-24].

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Key words: Eosinophilia, adrenal insufficiency, severe septic shock

List of Abbreviations:

ICU	Intensive Care Unit
WBC	White blood cells
SOFA	Sequential Organ Failure Assessment Score
APACHE II	Acute Physiology and Chronic Health Evaluation II score
VAP	Ventilator-Associated Pneumonia
Eos	Eosinophils

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Corresponding author:

Eleni Mouloudi,

85 Mantineas street, PC 54248,

Thessaloniki, Greece

tel.: +302310330049, +306949195810,

fax: +302310892358,

e-mail: elmoulou@yahoo.gr