



## Adrenal Insufficiency in Septic Patients Admitted to Intensive Care Unit: Prevalence and Associated Factors

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### Abstract

**Background:** Adrenal insufficiency (AI) is associated with an increase in the risk of mortality in ICU-admitted septic patients. It should be suspected not only in patients with septic shock but also in those with sepsis. The aim of this study was to investigate the prevalence of AI in the spectrum of septic patients and determine the main predictors of this condition.

**Methods:** This study included 99 patients with the diagnosis of sepsis, severe sepsis, or septic shock. Patients with basal cortisol < 10 µg/dl or those with Δ cortisol < 9 µg/dl after the cosyntropin test were considered as having AI. Appropriate statistical tests were used for comparing the variables between the two groups. A logistic regression model was applied to determine the predictors of AI. The P-value <0.05 was considered as a significant level.

**Results:** AI was found in 25 (25.3%) of these patients. There was no significant difference in the occurrence of AI in patients with sepsis, severe sepsis, or septic shock. Patients with positive blood culture (OR (95% CI); 7.8 (3.5-9.1); p=0.021) or those with CRP≥ 3+ (OR (95% CI); 14.1 8 (5.7-16.2); p<0.001) were more likely to develop AI.

**Conclusion:** AI is prevalent among ICU admitted septic patients even in the absence of septic shock. The main predictors of AI are high levels of CRP and positive blood culture.

**Keywords:** Adrenal Insufficiency, Sepsis, Septic Shock, C-Reactive Protein (CRP)

**Conflicts of Interest:** None declared

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### Introduction

Sepsis, a common disorder in hospitalized patients, is associated with a high mortality rate (1). Furthermore, even those who survive this acute illness may suffer from a substantial decline in cognition (2) and reduced quality of life (3).

An intact hypothalamic-pituitary-adrenal (HPA) axis is crucial for a normal response to any kind of stress such as sepsis. Activation of the HPA axis during stress is mainly mediated by corticotrophin-releasing hormone (CRH) independent pathways, including immune mediators (4).

However, HPA response to severe infection may alter during sepsis. This alteration may be induced by several mechanisms including irreversible damage to neuroendocrine cells, decreased CRH/adrenocorticotropin hormone (ACTH) synthesis /release, decreased steroidogenesis, reduced sensitivity to ACTH, a decline in cortisol delivery to tissues, and a decrease in binding capacity and affinity of glucocorticoid receptors (4). Consequently, disruption of the HPA axis in sepsis may lead to organ failure and eventually mortality (4).

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#### ↑What is “already known” in this topic:

Adrenal insufficiency (AI) is known as a frequent complication of such critical illnesses as severe sepsis, and can be associated with a worse outcome. However, the prevalence and diagnosis of AI in the critically ill patients remain controversial.

#### →What this article adds:

AI is common in a spectrum of septic patients admitted to ICU from mild sepsis to septic shock. High CRP and bacteremia are more likely to be associated with AI in these patients.

On the other hand, the prevalence and diagnosis of adrenal insufficiency (AI) in critically ill patients remain controversial. AI is estimated to occur at the rate of 25%-40% in the patient with septic shock (5), depending on the diagnostic test and the threshold applied for the diagnosis of AI. Moreover, identification of this disorder and its predisposing factors in ICU-admitted patients is important for assessing the burden of disease and planning the best therapeutic options in a specified population. Thus, we conducted a study to investigate the prevalence of AI and its associated factors among patients admitted to the medical Intensive Care Unit (ICU) due to sepsis.

## Methods

This is a cross-sectional study carried out in the Medical ICU at one of the specialty hospitals in Tehran, Iran. All adult patients admitted to the medical ICU and who met the criteria for sepsis/septic shock defined by the American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference were included in the study (6). Sepsis was defined as a systemic inflammatory response syndrome (SIRS) with a possible or established source of infection. Severe sepsis was defined as sepsis with one or more signs of organ dysfunction including the cardiovascular system, renal system, respiratory system, hematological system, unexplained metabolic acidosis, or inadequate fluid resuscitation. Septic shock was defined as sepsis with hypotension (systolic blood pressure <90 mmHg, or 40 mmHg less than patient's normal blood pressure) for at least 1 h in spite of adequate fluid resuscitation or need for vasopressors to maintain systolic blood pressure  $\geq$  90 mmHg. Patients with prior history of adrenal insufficiency (AI), those who suffered from HIV infection or tuberculosis, and patients who received any regular dose of corticosteroids, etomidate, ketoconazole or other medications known to suppress the adrenal function were excluded. Informed written consent was obtained from the first-degree relatives of the patients. The study adhered strictly to the principles of the Declaration of Helsinki, and approval from the local ethics committee was also obtained.

Demographic information (sex, age) and laboratory data, measured at the time of admission, including white blood cell count (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), results of blood culture, and severity of sepsis were recorded.

Patients who met the including criteria for sepsis/ septic shock underwent high dose (250  $\mu$ ) corticotropin stimulation testing (cosyntropin test) within 24 hours of admission to the medical ICU. After a baseline serum cortisol concentration was obtained, the patient received 250 $\mu$ g of corticotropin through the intravenous route. Post-stimulation serum cortisol concentration was drawn after 60 min of corticotropin injection. Serum cortisol levels were measured using radioimmunoassay kits (RIA). The cortisol increment levels were determined ( $\Delta$ , T60-T0). Patients were considered to have AI if delta cortisol after cosyntropin (250- $\mu$ g) administration was < 9  $\mu$ g/dl or random plasma cortisol was < 10  $\mu$ g/dl (7).

## Statistical analysis

Continuous variables are presented as mean  $\pm$  standard deviation (SD), and categorical variables are expressed as percentage. Independent Student t-test, Mann-Whitney U-test, and Chi-square test were used, as appropriate, to compare the variables between the two groups. The odds ratio (OR, 95% confidence interval) was calculated by logistic regression analysis.  $P \leq 0.05$  was considered statistically significant.

## Results

During a 12-month period of study (2014-2015), 106 patients including 60 (56.6%) men and 46 (43.4%) women, who met the criteria for sepsis and were admitted to the medical ICU were included. The mean age of patients was  $55.3 \pm 21.7$  years. The mean value of WBC was  $15326 \pm 3469$ . The mean ESR was  $44.6 \pm 17.2$  mm/h. All patients showed to have positive CRP of different degrees. Blood culture was positive in 8.6% of patients. A large proportion of patients suffered from sepsis (n= 60, 56.1%) while severe sepsis and septic shock were diagnosed in 30.5% (n= 32), and 13.4% (n= 14) of patients, respectively (Table 1). Of the 106 patients with the diagnosis of sepsis, 99 subjects underwent the corticotropin stimulation test. Adrenal insufficiency was found in 25 (25.3%) of these patients. Mean cortisol level before and after cosyntropin test was  $32.3 \pm 15.9$   $\mu$ g/dl and  $53.5 \pm 11.9$   $\mu$ g/dl, respectively ( $p=0.001$ ).

We compared the clinical characteristics of septic patients with and without AI (Table 2). There was no significant difference in the mean age of patients with and without AI (52.09 vs. 56.9 years,  $p=0.071$ ). Compared to the patients without AI, the patients with AI were more likely to be men (53.4% vs. 70.8%). However, it did not reach statistical significance ( $p= 0.120$ ). There was also no significant difference in WBC count (15610 vs 15140 cell  $\times$  1000/ $\text{mm}^3$ ;  $p= 0.084$  and ESR (45.25 vs 44.64 mm/h;  $p= 0.080$ ) between two groups. There was no significant difference in the distribution of different types of sepsis according to the presence or absence of AI ( $p= 0.124$ ).

**Table 1.** Baseline characteristics of patients with sepsis admitted in ICU

Variable	Statistic
Age (yrs)	$55.3 \pm 21.7$
Sex (M)	60 (56.6%)
WBC (cell $\times$ 1000/ $\text{mm}^3$ )	$15326 \pm 3469$
ESR (mm/h)	$44.6 \pm 17.2$
CRP	
1+	4 (2.4%)
2+	32 (30.5%)
3+	37 (35.4%)
4+	33 (31.7%)
Blood culture (% positive)	9 (8.6%)
Sepsis classification (%)	
Sepsis	60 (56.1%)
Severe sepsis	32 (30.5%)
Septic shock	14 (13.4%)
Baseline cortisol level ( $\mu$ /dl)	$32.3 \pm 15.9$
Stimulated cortisol level $\mu$ /dl	$53.5 \pm 11.9$

Data are presented as mean (standard deviation) or number (percentage) ICU; intensive care unit, WBC; white blood cell, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein

**Table 2.** Clinical characteristics of septic patients with and without adrenal insufficiency

Variable	Patients with AI (N=25)	Patients without AI (N= 74)	p-value
Age (yrs)	52.09 ± 22.7	56.92 ± 21.20	0.071
Sex (% M)	18 (70.8%)	40 (53.4%)	0.120
WBC (cell × 1000/mm <sup>3</sup> )	15610 ± 3256	15140 ± 3506	0.084
ESR (mm/h)	45.25 ± 12.17	44.64 ± 18.82	0.080
CRP (%)			<0.001
<3+	2 (5%)	32 (42.6%)	
≥ 3+	24 (95%)	32 (57.4%)	
Blood culture (% Positive)	5 (21.1%)	2 (3.3%)	0.021
Sepsis classification (%)			0.124
Sepsis	10 (40%)	46 (62.3%)	
Severe sepsis	10 (40%)	19 (26.2%)	
Septic shock	15 (20%)	8 (11.5%)	

Data are presented as mean (standard deviation) or number (percentage)

AI; adrenal insufficiency, WBC; white blood cell, ESR; erythrocyte sedimentation rate, CRP; C-reactive protein

However, patients with AI showed significantly higher levels of CRP ( $p < 0.001$ ), and they were more likely to have positive blood culture (21.1% vs. 3.3%,  $p = 0.021$ ). Binary logistic regression models showed the patients with positive blood culture had a higher likelihood of AI than patients with negative blood culture (odds ratio (95%CI); 7.8 (3.5-9.1);  $p = 0.021$ ). Moreover, patients with  $CRP \geq 3+$  were more likely to develop AI compared to those with  $CRP < 3+$  (odds ratio (95% CI); 14.1(5.7-16.2);  $p < 0.001$ ).

### Discussion

In this study, the prevalence of AI among ICU-admitted septic patients was estimated to be 25.3%. Moreover, patients with higher levels of CRP and those with positive blood cultures were more likely to develop AI.

The prevalence of AI in this study is less than some previous ones (8, 9). The reported prevalence of AI varies in a wide range across the studies depending on the studied population, underlying disease, severity of illness, specific tests, and the threshold for diagnosis of AI. Although high dose (250 µg) cosyntropin test has been confirmed to be superior to the other existing diagnostic tests for establishing AI (10), there is still no consensus on whether the ACTH stimulation test is superior to random cortisol for the routine diagnosis of AI in the critically ill patients (7). It is unlikely that a single test can reliably diagnose AI because AI during sepsis may be induced by several mechanisms such as alteration in the cortisol synthesis or metabolism, or tissue resistance to the cortisol. In this study, both random cortisol less than 10 µg/dl and delta cortisol less than 9 µg/dl after cosyntropin (250 µg) administration were considered as AI. Moreover, we found that the prevalence of AI did not differ across the spectrum of sepsis. Although several studies showed the more severe sepsis is associated with the lower levels of basal cortisol (9, 11), a more recent study indicated high un-stimulated cortisol, but not low, is associated with disease severity (12). Furthermore, recent results from a large European multicenter study conducted among patients with severe sepsis and septic shock revealed that patients who did not survive this critical illness had higher baseline cortisol levels but a blunted response to ACTH compared with the survivors (13). This finding supports the fact that

both impaired cortisol secretion and tissue resistance to cortisol could be the possible mechanisms underlying AI during sepsis. However, the prevalence of AI in critical illness might be overestimated because of limited evaluation tools. In some centers, a rise in blood pressure (BP) following administration of hydrocortisone in patients with septic shock has been considered as evidence for AI, while it may not be due to AI and maybe only a vascular interaction (14).

In addition, we investigated the factors associated with AI among the ICU-admitted septic patients. We found no relationship between age and sex of the patients and the occurrence of AI in septic patients. Few studies have investigated the association of age and sex with the occurrence of AI during sepsis. One study reported a higher rate of AI in younger-aged septic patients (8). Another study demonstrated that AI is common in elderly patients with septic shock (15). However, this study evaluated the prevalence of AI in septic patients for more than 70 years. A more recent study assessed the prevalence of adrenal crisis in general practice settings. This study indicated among patients with no history of chronic AI those who were older and had more comorbidity were more likely to develop adrenal crisis (16). Although we found no gender difference in the occurrence of AI in ICU-admitted septic patients, a previous study showed female gender is an independent protective factor for the occurrence of AI in mechanically-ventilated, critically ill patients. The possible explanation for this finding is the lower prevalence of sepsis in women compared to men (17). However, the discrepancy in these results might be due to the difference in the studied population and geographical or racial factors.

When we investigated the role of routine inflammatory markers in the development of AI during sepsis, we found there is no difference in the level of ESR as well as WBC count between septic patients with and without AI. However, patients with higher levels of CRP and those with positive blood cultures were more likely to develop AI. Pro-inflammatory cytokines have been suggested to compete with corticotropin at its receptor (18) or induce tissue resistance to glucocorticoids (19). On the other hand, such inflammatory factors as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), may be responsible for the

activation of the HPA axis during sepsis (20). Leukocytosis and increased CRP have also been reported to be associated with AI (21). Our study showed the association between CRP, but not WBC count, and AI. Similar to another study (9), positive blood culture was associated with an increase in the risk of AI in our patients. However, stress-related illness during sepsis is mediated by different mechanisms. Moreover, both environmental and genetic factors can induce glucocorticoid resistance. Thus, it is not surprising that this condition varies greatly in the presentation in different individuals and populations. Identification of inflammatory markers associated with an increased risk of AI is of great importance in that they can be applied as predictors of AI in critically ill patients.

In contrast to most previous studies that focused on the evaluation of AI in septic shock, we investigated the prevalence of AI and its associated factors in the spectrum of sepsis. Moreover, to define AI, we applied both basal cortisol levels of  $<10$   $\mu\text{g/dl}$  and an incremental level of  $<9$   $\mu\text{g/dl}$  after stimulation. In addition, we examined the inflammatory markers, routinely checked in septic patients, as predictors of AI. However, our study was performed in a single medical center and comprised of a small number of subjects.

### Conclusion

In summary, this study demonstrated AI is common in a spectrum of septic patients admitted in ICU, and physicians should search for AI in septic shock, severe sepsis, or even sepsis especially when CRP is elevated or blood cultures are positive.

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### Conflict of Interests

The authors declare that they have no competing interests.

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