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Low Cortisol Levels as a Cause of Hypotension During Extended ICU Stay

Uzamış Yoğun Bakım Yatışı Sırasında Gelişen Hipotansiyon Sebebi Olarak Düşük Kortizol Seviyeleri

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ABSTRACT

Aim: To determine the prevalence of newly developed low cortisol levels among critically ill medical patients with prolonged or recurrent vasopressor need as well as the factors associated with it.

Materials and Methods: This was an observational study which was conducted in a university hospital's medical intensive care unit (ICU) between July 2014 - July 2015. Initial cortisol levels were measured in septic shock patients unresponsive to fluid resuscitation and vasopressors. Patients with initial cortisol levels ≥15 µg/dl were followed; testing was repeated in patients with ongoing/recurrent vasopressor dependency. Patients were grouped as higher (≥15 µg/dl) and lower (<15 µg/dl) cortisol groups based on repeat testing.

Results: Thirty-seven patients had initial cortisol levels ≥15 µg/dl and 19 patients underwent cortisol retesting for ongoing/recurrent vasopressor need. Mean (±SD) age of the patients was 70±13.5 years. APACHE II and Sequential Organ Failure Assessment scores on ICU admission were 25.3±6.5 and 10.4±5.2, respectively. Eleven (%58) were in the lower cortisol group. Age, gender, admission APACHEII and SOFA scores, serum albumin, protein, C-reactive protein and procalcitonin levels at time of admission and repeat sampling were similar between the groups. However, at the time of cortisol retesting, patients with lower cortisol levels had significantly longer length of ICU stay (p=0.038). When glucocorticoid therapy was begun in lower cortisol group, vasopressors were weaned within 48 hours in all.

Conclusion: Prolonged or recurrent vasopressor dependency should prompt a search for low cortisol levels in patients with prolonged critical illness, even though prior results were reported to be normal.

Key words: Critical Illness,Cortisol,Septic Shock,Vasoconstrictor Agents

ÖZ

Amaç: Uzamış veya tekrarlayan vazopressör ihtiyacı olan medikal kritik hastalarda yeni gelişen düşük kortizol seviyelerinin ve ilişkili faktörlerin belirlenmesi

Materyal ve Method: Bu gözlemsel çalışma bir üniversite hastanesi dahili yoğun bakım ünitesinde (YBÜ) Haziran 2014-Haziran 2015 tarihleri arasında gerçekleştirildi. Başlangıç kortizol seviyeleri sıvı ve vazopressör tedaviye yanıtsız septik şok hastalarında ölçüldü. Başlangıç kortizol düzeyi ≥15 µg/dl olan hastalar takibe alınarak devam eden veya yeniden gelişen vazopressör ihtiyacı halinde test tekrar edildi. Hastalar tekrarlanan test sonuçlarına göre yüksek (≥15 µg/dl) ve düşük (<15 µg/dl) kortizol gruplarına ayrıldılar.

Bulgular: Otuz-yedi hastada başlangıç kortizol düzeyi ≥15 µg/dl idi ve 19 hasta devam eden/tekrarlayan vazopressör ihtiyacı nedeniyle tekrar test edildi. Ortalama yaş 70±13.5(±SD)idi. YBÜ kabulündeki APACHE II ve ardışık organ yetmezliği değerlendirme skoru (SOFA) 25.3±6.5 ve 10.4±5.2 olarak hesaplandı. On-bir (%58) hasta düşük kortizol grubundaydı. Yaş, cinsiyet, giriş APACHE II ve SOFA skorları kabulde ve tekrar örnekleme sırasındaki serum albumin, protein, C reaktif protein ve prokalsitonin seviyeleri her iki grupta benzerdi. Ancak kortizol tekrar örneklemesi sırasında düşük kortizol grubundaki hastaların yoğun bakım yatış süreleri anlamlı olarak uzundu (p=0.038). Düşük kortizol grubunda glukokortikoid tedavi başlanmasının ardından tüm hastalarda vazopressör tedavisi 48 saat içinde kapatıldı.

Sonuç: Uzamış veya tekrarlayan vazopressör ihtiyacı olan uzamış kritik hastalık tablosunda önceki sonuçlar normal raporlanmış olsada hastalar düşük kortizol seviyeleri açısından taranmalıdır.

Anahtar kelimeler: Uzamış kritik hastalık, kortizol, septik şok, vazopressör ajanlar

Introduction

Changes in cortisol metabolism and adrenal functions during critical illness have gained much attention, especially after the study by Annane et al., which has shown that some patients develop critical illness related adrenal dysfunction early during the course of sepsis (1). Studies have reported that low dose steroids were effective to reverse the shock state in certain patients with sepsis (2,3). Likewise, low-dose steroids were recommended to septic shock patients who were unresponsive to fluids and vasopressors in the Surviving Sepsis Campaign Guidelines (4). Still, there are uncertainties on evaluation and treatment of critical illness related corticosteroid deficiency and it is an area of ongoing debate (5-8). Currently, sepsis guidelines strictly limit recommendation of steroids to patients with septic shock in the acute phase, if hemodynamic instability persist after adequate fluid resuscitation therapy and vasopressors (9).

After an acute stressful event, elevation of cortisol level, which is the result of changes in the hypothalamic-pituitary-adrenal axis (HPA), is physiologic. Initially, this response is mainly maintained by ACTH-independent increased release of cortisol and thereafter decreased cortisol breakdown (10). Lower cortisol levels during the earlier phases of septic shock require corticosteroid replacement. However, HPA response to stress is a dynamic process, and there are data to support that this response may be inadequate in the later phases of sepsis, as well (11-14). Data on the long-term progress of cortisol levels after the acute phase of critical illness are scarce.

The primary outcome of the study was to determine the prevalence of low cortisol levels in critically ill patients with prolonged/recurrent vasopressor need. Secondary outcomes were ICU mortality and determination of the factors that were associated with lower cortisol levels.

The preliminary results of this study has been presented in Italy on October 1-5, 2016 during 29th ESICM LIVES Congress as an e-poster.

Materials and Methods

This observational, prospective study was conducted after approval by the university institutional ethics committee (Reference number: l2-534-14) between July 2014 and July 2015. The research was conducted in accordance with the principles of the Helsinki Declaration. All adult patients (≥18 years) who developed septic shock during ICU admission or were admitted with a diagnosis of septic shock to the 9 bed medical intensive care unit (ICU) of a tertiary level, academic university hospital were included. Informed consent for this study was obtained from the septic patients' first degree relatives. Patients with septic shock, whose initial cortisol levels at the start of illness were higher than 15 µg/dl were followed, and cortisol testing was repeated in these patients upon ongoing/recurrent vasopressor dependency after appropriate treatment with no other underlying cause for hypotension.

Patients who were admitted with the diagnosis of septic shock were treated in line with the 2012 Surviving Sepsis Guidelines (15); intravenous, broad spectrum antimicrobials were administered within the first hour of septic shock, fluid resuscitation (at least 30 mL/kg of crystalloids) and vasopressor therapy after fluid loading (target mean arterial pressure (MAP) of 65 mm Hg) were followed. If despite fluid resuscitation and concomitant vasopressor therapy hemodynamic stability was not achieved, then intravenous corticosteroid therapy was given as a continuous infusion after blood sampling was performed for total cortisol levels and was found to be lower than 15 µg/dl (6). Forty mg methylprednisolone which is the equivalent of 200 mg hydrocortisone was used since hydrocortisone was not readily available in Turkey during the study period.

Total cortisol testing was performed to septic shock patients who were refractory to vasopressors and volume resuscitation on admission if they were not on steroids for other reasons. For patients with initial cortisol levels ≥15 µg/dl, cortisol testing was repeated if vasopressors could not be weaned despite treatment of the underlying condition or recurrent need for vasopressor occurred and no other underlying cause could be found for the hemodynamic instability after extensive evaluation of the patient. Cardiological evaluation made with echocardiography, all possible focus for infection and infection parameters checked for hemodynamic instability.

Initial cortisol levels in patients with septic shock were studied irrespective of time of the day, since diurnal variation is expected to be lost. Repeat cortisol testing was performed at 08:00 am in all patients. Measurement of the serum total cortisol levels were performed by using the standard spectrophotometric method (Roche E 170, USA).

Vasopressor dependent patients with repeat cortisol levels lower than 15 µg/dl were treated with 40 mg methylprednisolone as daily continuous infusion until vasopressors were discontinued. Subsequently, methylprednisolone doses were tapered over days and terminated depending on the patient's clinical course.

Recorded parameters were age, sex, comorbidities, APACHE II, Glaskow Coma Scale score, Sequential Organ Failure Assessment (SOFA) score, serum albumin, total protein, C-reactive protein (CRP) and procalcitonin levels (at the time of first and repeated cortisol sampling), interval between two cortisol sampling, length of ICU stay, ICU outcome and 28-day mortality.

For statistical analysis patients were grouped as higher and lower cortisol groups into two, based on their repeat cortisol levels (repeat cortisol level ≥15 µg/dl and <15 µg/dl, respectively). Cut-off levels are determined in accordance with other similar studies on adrenal dysfunction (11, 13-14). This cut-off level is also in accordance with the recently suggested algorithm for evaluation of adrenal insufficiency during critical illness by the *American Association of Clinical Endocrinologists Adrenal Scientific Committee* (10).

Unless otherwise noted, continuous variables were presented as medians (interquartile range [IQR]). They were compared using Mann-Whitney U-tests for nonparametric variables. Categorical variables were analyzed with the $\chi 2$ test or in small sample sizes with the Fisher's exact test. Differences between basal cortisol levels and repeat cortisol levels were compared using the paired student t-test. Statistical significance was considered with a 2-tailed p value of less than 0.05. A software program was used to perform the statistical analysis (SPSS 15.0, SPSS, Chicago, Illinois).

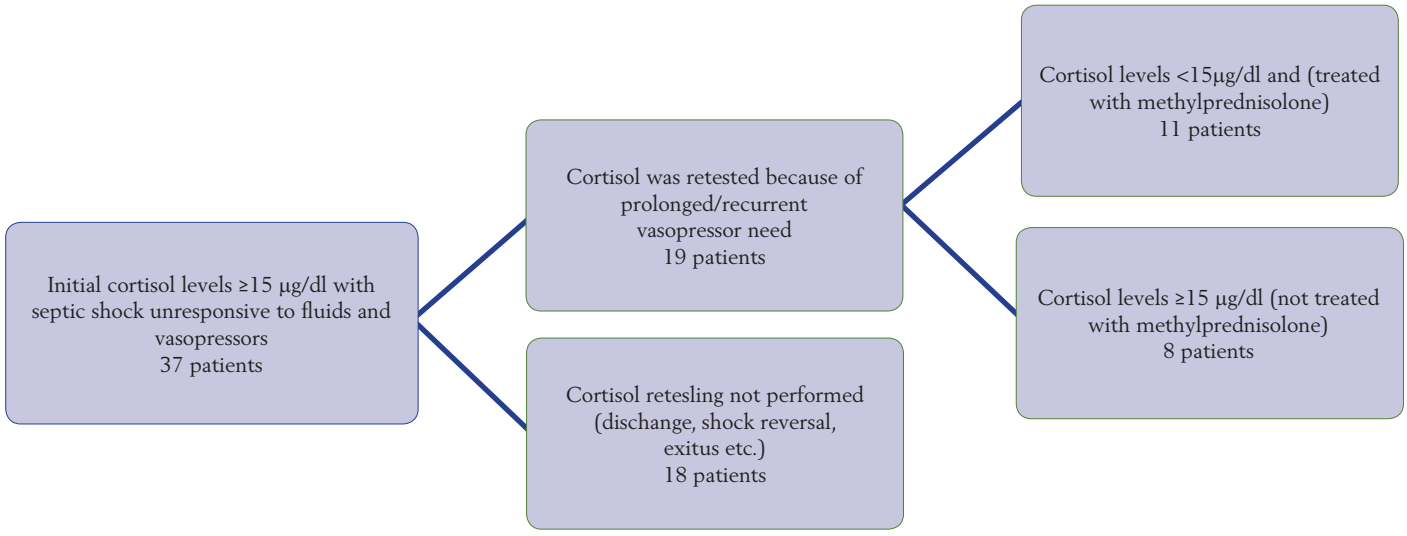

Figure 1. Flow chart of patients.

Results

A total of 120 patients were admitted to the medical ICU during the study time period. Of the patients admitted to the ICU 37 (30.8%) developed septic shock during ICU stay or were admitted with septic shock unresponsive to fluids and vasopressor therapy and were found to have initial cortisol levels higher than 15 µg/dl (Figure 1). Of these, 19 (51.4%) patients had prolonged or recurrent vasopressor need and were included in the study. They were re-tested for serum cortisol levels. Characteristics and comorbidities of these patients are presented in Table 1.

Of the patients included in the study, 14 (73.7 %) were male. Mean (± SD) age was 70 ± 13.5 years. Mean APACHE II and SOFA scores on ICU admission were 25.3 ± 6.5 and 10.4 ± 5.2, respectively. Initial and repeat serum cortisol levels of the groups are presented in Table 2. The admission cortisol levels were similar between groups. In the lower cortisol group (n=11) the mean initial (± SD) cortisol level was 26.6±12.8 µg/dl and mean repeated (± SD) cortisol level was 8.9±3.8 µg/dl. In some of the patients, total cortisol levels were even lower than 5 µg/dl. These patients were referred to endocrinology department for further work-up after ICU stay without ending steroid therapy. At the time of initial and repeat cortisol sampling serum albumin, total protein, CRP and procalcitonin levels were studied, as well. There was no significant difference between the two groups for these parameters at all times and these are listed in Table 2.

When groups were compared for factors associated with lower cortisol levels, no significant difference could be demonstrated. Regarding disease severity, no difference was found between groups. Demographic factors were also found to be similar between groups. The median interval between initial and repeat cortisol sampling was (median, IQR) 12(8-30) days. Although

Table 1. Characteristics and comorbidities of patients.

	Total (n:19)	Cortisol < 15 µg/dl (n:11)	Cortisol ≥ 15 µg/dl (n:8)	p
Age, years (mean ± SD)	70 ± 13.5	70.7 ± 13,5	69.1 ± 14.4	0.72
Male sex (%)	73.7	63.6	87.5	0.34
APACHEII score (mean ± SD)	25.3 ± 6.5	25.2 ± 6.8	25.5 ± 6.4	0.94
SOFA score (mean ± SD)	10.4 ± 5.2	9.9 ± 4.8	11.2 ± 6	0.60
Glaskow score (mean ± SD)	11.1 ± 4.6	9.9 ± 4.8	12.8 ± 4.1	0.18
Comorbidities (%)				
Diabetes mellitus	15.8	18.2	12.5	1.00
Congestive heart failure	26.3	27.3	25	1.00
Chronic renal failure	36.8	27.3	50	0.38
Chronic hepatic disease	5.3	0	12.5	0.42
Coronary artery disease	21.1	18.2	25	1.00
Chronic obstructive pulmonary disease	31.6	36.4	25	1.00
Malignancy	10.5	9.1	12.5	1.00
Length of ICU stay before re-sampling, days (median, IQR)	23.5	53.5 [61.2]	19.5 [18]	0.03
Interval between two cortisol samplings, days (median, IQR)	12 [8-30]	21 [20]	8.5 [5.7]	0.68
ICU mortality (%)	4 (21.1)	1 (9.1)	3 (37.5)	0.26

SD: standard deviation; **APACHE II:** acute physiology and chronic health evaluation; **SOFA:** sequential organ function assessment; **ICU:** intensive care unit, **IQR:** inter quarter range

Table 2. Laboratory results of patients at initial and second cortisol testing.

	Total (n:19)	Cortisol level < 15 µg/dl (n:11)	Cortisol level ≥15 µg/dl (n:8)	p
Cortisol (mean ± SD), µg/dl	t_0:28.6±12.3 t_1:16.7±10.1	t_0: 26.6 ± 12.8 t_1: 8.9 ± 3.8	t_0: 31.4 ± 11.8 t_1: 27.3 ± 4.4	0.42 <0.001
Albumin (mean ± SD), g/dL	t_0: 2.4 ± 0.4 t_1: 2.4 ± 0.4	t_0: 2.4 ±0.4 t_1: 2.3 ±0.4	t_0: 2.4 ± 0.2 t_1: 2.5 ± 0.5	0.89 0.59
Protein (mean ± SD), g/dL	t_0: 5.3 ±0.8 t_1: 5.3 ±0.7	t_0: 5.3 ±0.9 t_1: 5.5 ±0.6	t_0: 5.3 ±0.8 t_1: 5 ±0.7	0.95 0.11
CRP (median, IQR), mg/L	t_0:109.2 [65.3-221] t_1:107.9 [39.8-134.6]	t_0:116.9 [155.7] t_1: 54.9 [99.9]	t_0: 108.8 [178.6] t_1: 114.4 [109.7]	0.93 0.36
Procalcitonin (median, IQR), ng/mL	t_0:0.77 [0.15-6.06] t_1:0.66 [0.13-8.82]	t_0: 0.19 [5.79] t_1: 2.61 [11.57]	t_0: 0.13 [8.74] t_1: 0.88 [9.6]	0.13 0.44

t_0: first cortisol sampling time, **t_1:** second cortisol sampling time, **SD:** standard deviation; **IQR:** inter quarter range, **CRP:** C-reactive protein

interval between two samplings of the lower cortisol group seemed longer, there was not a statistically significant difference between groups. However, at the time of cortisol retesting, patients with lower cortisol levels had significantly longer length of ICU stay (p=0.038).

When methylprednisolone was administered to vasopressor dependent patients whose repeat cortisol levels were lower than 15 µg/dl; vasopressors were discontinued within 48 hours at most, in all patients. Vasopressor weaning was longer and varied in the higher cortisol group.

Median ICU length of stay was significantly longer in the lower cortisol group at the time of second sampling (p=0.038). Although ICU mortality rate was lower in the lower cortisol group, statistically significant difference between groups was not present (9.1% vs 37.5%, p=0.262).

Discussion

In this study, a subgroup of patients with initial cortisol levels higher than 15 µg/dl and recurrent or prolonged need for vasopressors during ICU stay have been demonstrated to have low total cortisol levels, and their hemodynamic status has responded to treatment with corticosteroids. Current research about chronic critical illness is not adeqaute to clarify exact mechanisms involved. This study may be one of the preliminary studies to demonstrate that at least in a group of critically ill patients with prolonged vasopressor need, new onset corticosteroid deficiency may be the cause and may respond favorably to steroid therapy.

There were some observations that cortisol levels decreased with prolonged illness, and this condition was named as adrenal exhaustion. (12-14) Guzman et al. identified a group of 13 patients whose cortisol levels were repeated after a mean of 6 days because of ongoing vasopressor dependency (12). They found that these patients had decreased cortisol levels in their follow up and responded to steroids. Marik et al. studied another group of patients with liver failure in ICU (13). They reported 16 liver failure patients with normal initial cortisol levels but who failed to improve. When cortisol levels were repeated they were found to be lower. Meanwhile, Vassiliadi et al. have longitudinally assessed the adrenal functions in a group of septic patients for a month (16). Their results showed that severity of illness affected total cortisol levels, however it did not change during the course of illness. They did not consider adrenal dysfunction to be an important problem during prolonged phases of illness as evaluated by cosyntropin stimulation test (CST). However, some of the patients were not on vasopressors during study enrollment, and their APACHE II scores and baseline cortisol levels were lower indicating a less severity of patients.

How to diagnose and treat corticosteroid insufficiency in critically ill medical patients, especially if they are in septic shock, is a diagnostic conflict (10,17). There have been many studies on evaluation of the cortisol metabolism and adrenal functions during critical illness. Elevated cortisol levels during critical illness have been related to pituitary-independent adrenal stimulation by cytokines and other factors, and a decrease in catabolism of cortisol. They have not been related to ACTH induced cortisol release by the adrenals (10,16). Initially, CST was offered to diagnose adrenal insufficiency during critical illness (11). Subsequently, it was realized that in critical illness, CST was not appropriate due to the complexity of interpretation of the results and other factors that may influence the reponse of the adrenals (10,18). Meanwhile, measuring total cortisol levels have been criticized for not taking into account the decreased level of cortisol binding proteins during the acute phase of critical illness. However, routine utilization of free cortisol levels was not supported due to inadequate evidence and difficulties in routinely performing the test. Still, testing for total cortisol levels has been the most widely utilized test for screening adrenal insufficiency, despite ongoing debates (10, 15, 18).

One of the many handicaps of measuring total cortisol levels is that, total cortisol levels may be significantly low despite normal free cortisol levels, especially in hypoproteinemic patients. Concerning this issue, in our study, we have demonstrated that serum protein and albumin levels were similar between groups at both times of sampling.

It has been demonstrated that corticosteroids could be of value in reversing septic shock, despite absence of a demonstrable adrenal insufficiency (5). Some of the effects of corticosteroids on

hemodynamics have been explained by their effects on vascular hyporeactivity (5,19,20). Improved hemodynamics may be the result of anti-inflammatory action of corticosteroids as well. Expression of proinflammatory cytokines, mediators, and their receptors are inhibited by the corticosteroids. This contributes to their anti-inflammatory actions (21). This may be an important issue when trying to manage dysregulated systemic inflammation.

Kwon et al. has reported that for relative adrenal insufficiency, SOFA score could be an independent risk factor (22). However, no correlation between disease severity and low cortisol levels was found in our study. As well, the degree of inflammation as demonstrated by CRP and procalcitonin levels were similar between the groups. We could not identify a risk factor for adrenal dysfunction in our study group. The groups were similar except that lower cortisol group had prolonged ICU stay before and longer interval time to repeat cortisol testing than the other group.

On the other hand, there is a growing recognition of a group of patients, who need prolonged support in the ICU and are hard to wean from intensive care support therapies. Although many different mechanisms and pathways seem to be involved; persistent inflammation, immune suppression and catabolism are considered to be the main basis of this state. Recently, it has been called as persistent inflammation, immunosuppression and catabolism syndrome (PICS) (23). Although, this was not the group of patients targeted in our study, when the diagnostic criteria for PICS are reviewed, it can be observed that the study patients meet the criteria for PICS. They have been in ICU for more than 14 days, have prolonged need for mechanical ventilation, vasopressor support cannot be weaned. Mean CRP levels are high indicating persistent inflammation and albumin levels are low indicating a catabolic process. Although our study group was limited, administration of steroids seemed to improve their outcome if their cortisol levels were low. Was prolonged critical illness the cause of low cortisol levels as a part of multiple organ dysfunction or was low cortisol levels contributing to prolonged critical illness? This study may be considered a preliminary step to a well-designed study to further evaluate HPA and effects of steroids in patients with PICS.

There are several limitations of this study. First is the limited number of patients. This may have affected the results of statistical analysis. Secondly, total cortisol levels were being measured to screen for corticosteroid insufficiency. Presence of free cortisol levels and perhaps CST results would have been more comprehensive. Thirdly, despite guidelines, little is defined precisely regarding critical illness related corticosteroid insufficiency, especially during the later phase in the disease course. Lastly, PICS had not been defined at the start of our study, although retrospectively all included patients conform to criteria of PICS. This limits the extrapolation of our findings to patients with PICS, although, we believe it may add to the limited data on cortisol levels and its clinical implications during the course of prolonged critical illness.

Conclusion

During the course of critical illness, both cortisol metabolism and the responses of the adrenal glands are dynamic processes. We suggest retesting cortisol levels in patients who have prolonged critical illness and vasopressor dependency. Identifying patients that could benefit from corticosteroid therapy may be an important issue in their management.

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AUTHOR CONTRIBUTIONS:

Concept: LT, GG, NDA; **Design:** LT, NDA; **Supervision:** NDA; **Resources:** LT,NDA,GG; **Materials:** LT,GG **Data Collection and/or Processing:** LT,GG; **Analysis and/or Interpretation**: LT,NDA; **Literature Search:** LT; **Writing Manuscript**: LT, NDA; **Critical Review:** NDA.

YAZAR KATKILARI:

Fikir: LT, GG, NDA; **Tasarım:** LT, NDA; **Denetleme:** NDA; BB; **Kaynaklar:** LT,NDA,GG; **Malzemeler:** LT,GG; **Veri Toplanması ve/veya İşlemesi:** LT,GG; **Analiz ve/veya Yorum:** LT,NDA; **Literatür Taraması:** LT; **Yazıyı Yazan:** LT, NDA; **Eleştirel İnceleme:** NDA.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara University (Approval Date: 13.06.2014, reference no: 12-534-14).

Informed Consent: Written informed consent was obtained from relatives of patients or patients who participated in this study.

Peer-review: Externally peer-reviewed.

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29th ESICM LIVES Congress as an e-poster in Italy

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References

1. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71. [CrossRef]
2. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003;167:512-20. [CrossRef]
3. Oppert M, Schindler R, Husung C, Offermann K, Gräf KJ, Boenisch O, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. Crit Care Med 2005;33:2457-64. [CrossRef]
4. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004;32:858-73. [CrossRef]
5. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. New Engl J Med 2008;358:111-24. [CrossRef]
6. Annane D, Renault A, Brun-Buisson C, Megarbane B, Quenot JP, Siami S, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. N Engl J Med 2018;378:809-18. [CrossRef]
7. Venkatesh B, Finfer S, Cohen J, Rajbhandari D, Arabi Y, Bellomo R, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. N Engl J Med 2018;378:797-808. [CrossRef]
8. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 2017;43:1751-63. [CrossRef]
9. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486-552. [CrossRef]
10. Hamrahian AH, Fleseriu M. AACE Adrenal Scientific Committee. Evaluation and management of adrenal insufficiency in critically ill patients: disease state review. Endocr Pract 2017;23:716-25. [CrossRef]
11. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36:1937–49. [CrossRef]
12. Guzman JA, Guzman CB. Adrenal exhaustion in septic patients with vasopressor dependency. J Crit Care 2007; 22: 319–23. [CrossRef]
13. Marik PE. Adrenal-exhaustion syndrome in patients with liver disease. Intensive Care Med 2006;32:275-80. [CrossRef]
14. Wu JY, Hsu SC, Ku SC, Ho CC, Yu CJ, Yang PC, et al. Adrenal insufficiency in prolonged critical illness. Crit Care 2008;12:R65. [CrossRef]
15. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637. [CrossRef]
16. Vassiliadi DA, Dimopoulou I, Tzanela M, Douka E, Livaditi O, Orfanos SE, et al. Longitudinal assessment of adrenal function in the early and prolonged phases of critical illness in septic patients: relations to cytokine levels and outcome. J Clin Endocrinol Metab 2014; 99: 4471-80. [CrossRef]
17. Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab 2006;91:3725-45. [CrossRef]
18. Boonen E, van den Berghe G. Mechanisms in endocrinology: new concepts to further unravel adrenal insufficiency during critical illness. Eur J Endocrinol 2016;175(1):R1-9. [CrossRef]
19. Loriaux DL, Fleseriu M. Relative adrenal insufficiency. Curr Opin Endocrinol Diabetes Obes 2009;16:392-400. [CrossRef]
20. Yang S, Zhang L. Glucocorticoids and vascular reactivity. Curr Vasc Pharmacol 2004;2:1-12. [CrossRef]
21. Meduri GU, Muthiah MP, Carratu P, Eltorky M, Chrousos GP. Nuclear factor-kappaB and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. Neuroimmunomodulation 2005;12:321-38. [CrossRef]
22. Kwon YS, Kang E, Suh GY, Koh WJ, Chung MP, Kim H, et al. A prospective study on the incidence and predictive factors of relative adrenal insufficiency in Korean critically-ill patients. J Korean Med Sci 2009;24:668-73. [CrossRef]
23. Mira JC, Brakenridge SC, Moldawer LL, Moore FA. Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS). Crit Care Clin 2017; 33: 245–58. [CrossRef]