Original Article

Prevalence and Predictive Factors of Adrenal Insufficiency in Septic Shock Patients

Weravut Mingkuan MD[1], Suwipa Debukkam MSc[2]

[1] Division of Pulmonary and Tuberculosis, Department of Internal Medicine, Uttaradit Hospital, Uttaradit, Thailand
[2] Division of Clinical Chemistry and Clinical Pathology, Uttaradit Hospital, Uttaradit, Thailand

Objective: To determine prevalence, risk factor and survival time associated with adrenal insufficiency [AI] in septic shock patients.

Materials and Methods: The prospective study was performed in all septic shock patients admitted within 24 hours with shock at the medical ward and medical intensive care unit between May 2016 and May 2017. Demographic data, clinical information, and cumulative survival time of patients were collected. Baseline cortisol was evaluated and followed by 1 microgram cosyntropin stimulation test. Serum cortisol was drawn at 30 and 60 minutes after injection, respectively. AI diagnosed by a level of cortisol increased less than 9 microgram/dl from baseline level or baseline cortisol less than 10 microgram/dl.

Results: One hundred twenty-two patients were recruited into the present study, and overall prevalence of AI was 56 (46%). Baseline serum cortisol between AI and no-AI groups were 17.7±7.7 microgram/dl versus 45.7±21.2 microgram/dl (p = 0.025). Predictive factors associated AI were herbal medicine used (OR 3.30, 95% CI 1.44 to 6.60, p = 0.002), serum CO_2 less than18 mEq/L (OR 1.15, 95% CI 1.08 to 1.25, p = 0.038) and CHF (OR 11.80, 95% CI 1.14 to 121.80, p = 0.039). The median survival time between septic shock with baseline cortisol less than 25 microgram/dl versus more than 25 microgram/dl were 21 days and 12 days (p = 0.028).

Conclusion: AI is common in septic shock patients that have used herbal medicine, serum CO_2 of less than 18 mEq/L, and CHF are useful risk factors during admission. In addition, the baseline cortisol level below 25 microgram/dl is associated with longer survival days.

Keywords: Prevalence, Risk factors, Adrenal insufficiency, Septic shock

J Med Assoc Thai 2018; 101 (11): 1591-7
Website: http://www.jmatonline.com

Adrenal insufficiency [AI] was frequently reported in critically ill patients with severe sepsis[1]. The prevalence in medical intensive care unit [ICU] patients varied widely depending upon population being selected and diagnostic criteria used[2-4]. Mechanisms have been proposed to explain AI including impaired hypothalamic-pituitary-adrenal [HPA] axis during critical illness, decreased production of corticotropin-releasing hormone [CRH], adrenocorticotropic hormone [ACTH], cortisol, and the dysfunction of their receptors[2,5,6].

The clinical characteristics and laboratory findings of AI lack specifics during septic shock, which make difficult to determine in ICU[1-3]. Physicians' awareness of this condition remained a problem in most urban hospitals because the clinical presentations vary on severity of disease. Furthermore, some hospitals have limitation in laboratory assessment. The diagnosis is based on serum cortisol level in response to ACTH stimulation test so-called Δ cortisol of less than 9 microgram/dl[1,2,7]. However, ACTH stimulation test takes time, requires three samples of blood, and is limited to be performed in the medical care setting.

Delay in diagnosis and corticosteroid treatment could increase the risk of death according to the recent study of CORTICUS that showed that patients receiving hydrocortisone had more rapid resolution of shock[8]. Additionally, the study of Annane et al[9] showed a 30% decrease in 28 days mortality in the hydrocortisone-fludrocortisone group. This benefit was confined to the group of non-responders (Δ cortisol of less than 9 microgram/dl)[9]. Currently, there are no variables that have identified AI during hospitalization. Therefore, the aims of the present study to evaluate prevalence and predicting factors including survival probability over the time associated to AI in septic shock patients.

Correspondence to:

Mingkuan W. Division of Pulmonary and Tuberculosis, Department of Internal Medicine, Uttaradit Hospital, Jessada Bodin Road, Tha It, Uttaradit 53000, Thailand.
Phone: +66-81-9087974, **Fax**: +66-55-832608
Email: mingkuan_v@hotmail.com

How to cite this article: Mingkuan W, Debukkam S. Prevalence and predictive factors of adrenal insufficiency in septic shock patients. J Med Assoc Thai 2018;101:1591-7.

Materials and Methods

Study design and patient population

The present prospective study was conducted in Uttaradit Hospital, the tertiary hospital in northern Thailand. The protocol was approved by the Hospital Ethic Committee and written informed consent was obtained from patients or their relatives. All consecutive patients with septic shock were enrolled if they admitted in medical ward and medical ICU within 24 hour between May 2016 and May 2017 and met the following criteria by the Surviving Sepsis Campaign Guideline, septic shock was sepsis induced hypotension, defined as a systolic blood pressure [SBP] of less than 90 mmHg or mean arterial pressure [MAP] of less than 70 mmHg or a SBP decrease greater than 40 mmHg or less than two standard deviations below normal for age in the absence of other causes of hypotension[10]. Patients with previous AI, prior received corticosteroid or drugs that may suppress HPA axis, and infection with human immunodeficiency virus from medical record were excluded.

Diagnosis of adrenal insufficiency

Within 24 hours after admission, the baseline cortisol was measured immediately, and then the 1 microgram cosyntropin stimulation test was performed by intravenously injection[3,11]. Blood samples were drawn at 30 and 60 minutes after injection for measurement of the total cortisol level. AI was diagnosed when baseline cortisol concentration was less than 10 microgram/dl or the difference between the baseline and the highest cortisol level at either 30 minutes or 60 minutes was less than 9 microgram/dl[2,7].

Data collection

The following parameters were recorded, demographic data including age, sex, underlying disease, and herbal medicine used. Clinical features including severity of disease assess by Simplified Acute Physiology [SAP] II score, MAP, clinical of steroid excess, central venous pressure [CVP], admission diagnosis, duration in hospital stay, and mortality rate. Laboratory variable including blood electrolytes, total white blood cells, neutrophil and platelet counts, serum levels of creatinine, glucose, magnesium, serum glutamic oxaloacetic transferase [SGOT], serum glutamic pyruvate transferase [SGPT], and blood culture.

Follow-up

All subjects diagnosed AI or No-AI were followed up for 60 days following study enrollment. The following data were recorded as laboratory assessment, hemoculture result, length of stays. Hospital death, and 60 days mortality.

Statistical analysis

Discrete and categorical variables were expressed as count with percentage, for continuous variables as mean ± standard deviation. Chi-square with the Fisher's exact test were used to compare the categorical data. Continuous variables were analyzed with the Student's t-test and the Mann-Whitney U test as appropriate. The logistic regression model was used to identify associated variables predictive factors as odds ratio [OR]. Compare the survival probability between septic shock which had random serum cortisol less than or more than 25 microgram/dl by log-rank test and presented with the Kaplan-Meier curve. All variables and statistics were analyzed by using Stata software, version 12.1 licensed serial number 20120500897. Probability value [*p*-value] of less than 0.05 indicated statistical significance. The sample size was calculated to have an 80% chance of detecting AI, with a significance of 5% as shown by previous research[1,7], and using a primary outcome of prevalence of AI in septic shock reported at 55% to 70%. The total sample size required was 136.

Results

Patients characteristics

One hundred twenty-two patients with septic shock met the eligibility for inclusion criteria in the present study and were included in the study. There were 72 males and 50 females. The mean age of patients was 67.5±13.2 years. Admission diagnosis were 41% of all patients had pneumonia, 22% had septic shock, and 14% had urinary tract infection [UTI], respectively. The mean of SAP II score was 54.5±15.5. Table 1 shows the baseline characteristics and results by univariate analysis of the patients with No-AI compared to those in the AI group. Admission diagnosis ($p<0.001$), herbal medicine used ($p = 0.002$), mean SAP II score ($p<0.001$), mean serum CO_2 ($p = 0.028$), and mean serum creatinine ($p = 0.033$) were statistically significant different between the group without and with AI. No significant differences between age, sex, preexisting disease, clinical of steroid excess, MAP, CVP, leukocyte count, neutrophil, platelet, sodium, potassium, serum glucose, magnesium, SGOT, SGPT, hemoculture, length of stay, and mortality rate was found. However, the mean of temperature trend

Table 1. Characteristics of patients according to the presence of adrenal insufficiency

Variables	Total (n = 122)	No-AI (n = 66)	AI (n = 56)	*p*-value
Age (year)	67.5±13.2	68.2±13.2	66.7±13.3	0.522
Sex: male	72 (59.0)	38 (57.6)	34 (60.7)	0.854
Admission diagnosis				<0.001
Septic shock	27 (22.1)	19 (28.8)	8 (14.3)	
Pneumonia	51 (41.8)	19 (28.8)	32 (57.1)	
UTI	18 (14.8)	9 (13.7)	9 (16.1)	
Meningitis	4 (3.3)	3 (4.5)	1 (1.8)	
Diarrhea	8 (6.6)	4 (6.1)	4 (7.1)	
SBP	4 (3.3)	3 (4.5)	1 (1.8)	
Others	10 (8.1)	9 (13.6)	1 (1.8)	
Preexisting disease				0.636
Hypertension	24 (19.7)	16 (24.2)	8 (14.3)	
IHD	7 (5.7)	5 (7.6)	2 (3.6)	
CHF	6 (4.9)	1 (1.5)	5 (8.9)	
Neurological disease	2 (1.6)	1 (1.5)	1 (1.8)	
Chronic lung disease	9 (7.4)	5 (7.6)	4 (7.1)	
Cancer	4 (3.3)	2 (3.0)	2 (3.6)	
Diabetes	10 (8.2)	5 (7.6)	5 (8.9)	
Liver disease	9 (7.4)	5 (7.6)	4 (7.1)	
None	51 (41.8)	26 (39.4)	25 (44.6)	
Herbal medicine use	50 (41.0)	19 (28.8)	31 (55.4)	0.002
Clinical of steroid excess				0.199
Moon face	26 (21.3)	8 (12.1)	18 (32.1)	
Buffalo hump	32 (26.2)	10 (15.2)	22 (39.3)	
Purplish striae	27 (22.1)	11 (16.7)	16 (28.6)	
SAPS II score	54.5±15.5	58.8±15.7	49.1±13.8	<0.001
Mean arterial pressure (mmHg)	56.4±7.9	57.4±8.8	55.1±6.5	0.115
CVP (mmH_2O)	14.6±4.2	15.4±4.0	13.5±4.4	0.176
Temperature (°C)	38.5±1.0	38.3±1.1	38.7±0.9	0.050
Lab finding				
Leukocyte (10^6/L)	15.7±8.2	15.6±9.4	15.5±6.6	0.935
Neutrophile	83.3±12.1	83.4±14.0	83.1±9.6	0.885
Platelet (10^9/L)	219.0±155.9	227.4±178.2	209.1±125.5	0.520
Sodium (mEq/L)	136.5±7.9	136.3±8.5	136.7±7.1	0.757
Potassium (mEq/L)	3.7±0.9	3.7±0.9	3.8±0.8	0.769
CO_2 (mEq/L)	21.8±0.0	20.0±7.3	24.0± 12.3	0.028
Creatinine (mg/dl)	2.5±2.4	3.0±2.7	2.1±1.8	0.033
Glucose (mg/dl)	121.4±86.4	135.0±67.9	116.8±97.1	0.818
Magnesium (mg/dl)	1.9±0.7	2.0±0.7	1.8±0.6	0.104
SGOT (mg/dl)	101.8±140.6	101.2±140.1	102.5±142.4	0.960
SGPT (mg/dl)	57.7±62.9	51.3±45.8	65.3±78.1	0.224
1 microgram cosyntropin test				
Baseline cortisol (microgram/dl)	32.9±21.5	45.7±21.2	17.7±7.7	0.025
Cortisol at 30 minutes (microgram/dl)	43.0±29.9	59.6±23.6	21.7 ±7.9	<0.001
Cortisol at 60 minutes (microgram/dl)	43.2±34.9	59.9±26.1	19.9±8.1	<0.001
Hemoculture positive	59 (48.4)	34 (51.5)	25 (44.6)	0.453
Length of stay (days)	15.2±16.5	14.8±15.1	15.6±17.5	0.927
60-days mortality	61 (50.0)	36 (54.6)	25 (44.7)	0.217

UTI = urinary tract infection; SBP = secondary bacterial peritonitis; IHD = ischaemic heart disease; CHF = congestive heart failure; SAP II = Simplified Acute Physiology Score II; CVP = central venous pressure; SGOT = serum glutamic oxaloacetic transferase; SGPT = serum glutamic pyruvate transferase; CO_2 = carbon dioxide

Values are presented as the mean ± SD or n (%)

was higher in AI than in the no-AI group (38.7±0.9 versus 38.3±1.1, $p = 0.005$).

One microgram corticotropin stimulation test

According to the criteria for diagnosis adrenal insufficiency, 56 (46%) patients had AI. The average age of AI patients was 66.7±13.3 years. There were 34 males and 22 females (61% and 39%). Comparing results of cortisol level among AI versus No-AI, the mean baseline cortisol was 17.7±7.7 microgram/dl

versus 45.7±21.2 microgram/dl; p = 0.025, the mean cortisol at 30 minutes was 21.7±7.9 microgram/dl versus 59.6±23.6 microgram/dl; $p<0.001$, the mean cortisol 60 minutes was 19.9±8.1 microgram/dl versus 59.9±26.1 microgram/dl; $p<0.001$. All parameters had statistical significant difference.

Predicting factors associated with adrenal insufficiency

Table 2 lists the predicting factors associated with adrenal insufficiency in septic shock, according to assessment. All the possible variables using logistic regression model analysis to obtained independent risk factors have been listed. Among those variables, congestive heart failure [CHF] was a strong independent risk factor of AI (adjustedOR 11.80, 95% CI 1.14 to 121.80, $p = 0.039$). The other potential risk factors to predict AI in septic shock during admission were herbal medicine used (adjustedOR 3.30, 95% CI 1.44 to 6.60, $p = 0.002$), and serum CO_2 less than 18 mEq/dL) (adjustedOR 1.15, 95% CI 1.08 to 1.25, $p = 0.038$). In addition, the authors found the independent protective risk factors of AI were SAP II (adjustedOR 0.64, 95% CI 0.47 to 0.86, $p = 0.003$) and serum creatinine of less than 2 mg/dl (adjustedOR 0.64, 95% CI 0.67 to 0.98, $p = 0.038$).

Survival of septic shock patients between baseline cortisol <25 microgram/dl vs. >25 microgram/dl

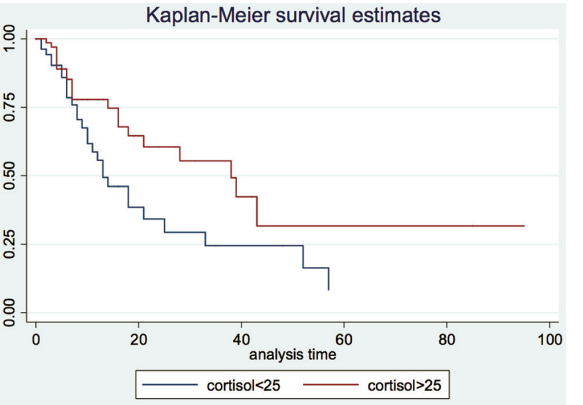
Figure 1 shows the cumulative probability of survival in subgroup of septic shock patients had level baseline cortisol cutoff at 25 microgram/dl estimated by univariate Kaplan-Meier analysis with log rank test. The median survival time baseline cortisol of less than 25 microgram/dl versus 25 microgram/dl were 21 days and 12 days ($p = 0.028$) with statistical significant difference.

Table 2. Predicting factors associated with adrenal insufficiency in septic shock

Factors	Odds ratio	95% CI	*p*-value
Univariate analysis*			
Herbal medicine use	3.07	1.45 to 6.49	0.003
CHF	10.00	1.00 to 100.61	0.050
SAP II	0.96	0.93 to 0.98	0.001
Serum creatinine <2 mg/dL	0.82	0.67 to 1.03	0.043
CO_2 <18 (mmol/dL)	1.05	1.00 to 1.10	0.038
Multivariate analysis†			
Herbal medicine use	3.30	1.44 to 6.60	0.002
CHF	11.80	1.14 to 121.80	0.039
SAP II	0.64	0.47 to 0.86	0.003
Serum creatinine <2 mg/dL	0.64	0.67 to 0.98	0.038
CO_2 <18 (mmol/dL)	1.15	1.08 to 1.25	0.038

CHF = congestive heart failure; SAP II = Simplified Acute Physiology Score II; CO_2 = carbon dioxide

* Logistic regression model was performed; † Reported by using adjusted odds ratio from logistic regression model after adjusting for age, sex, mean arterial pressure, and temperature



Kaplan-Meier curve of cumulative survival probability and length of hospital stay. A comparison in septic shock patients who survived until hospital discharge between the baseline cortisol level <25 microgram/dl had longer survival days than baseline cortisol level >25 microgram/dl (median survival time were 21 days vs. 12 days; $p = 0.028$) difference statistical significant by using log rank test.

Figure 1. Cumulative survival of septic shock patients among baseline cortisol <25 microgram/dl vs. >25 microgram/dl.

Discussion

AI in critical illness or severe infection are caused by impaired activation HPA axis that sustain secretion of corticotropin and cortisol[2,12]. Increased glucocorticoid action is an essential component of the general stress response[12,13]. In otherwise stable subjects, a random cortisol of less than 3 microgram/dl is suggestive of AI, whereas the presence a random cortisol of more than 19 microgram/dl may be ruled out[12]. However, because serum cortisol is usually elevated depending on the severity of illness, it is difficult to determine the appropriate cutoff level. A previous study demonstrated that baseline cortisol concentration of less than 25 microgram/dl should be the diagnostic threshold. The sensitivity of baseline cortisol of less than 25 microgram/dl could predict steroid responsiveness in 96%[13]. By using baseline cortisol level of less than or equal to 35 microgram/dl to diagnose AI, the sensitivity was 85%, specificity was 62%, and accuracy was 72% in Thai septic shock[14]. The present study demonstrated the reliable baseline cortisol at 17.7 microgram/dl as cutoff level for diagnosis AI. However, the past study used different level of cortisol criteria to diagnosis, so currently there is no universally accepted level[2,13].

In the present study, the authors selected the

baseline cortisol level of less than 10 microgram/dl or cortisol level increment less than 9 microgram/dl after low dose cosyntropin stimulation test were best reference to diagnosis of AI, from the data published by Annane et al[7], which showed high specificity of test but low sensitivity. The study used overnight single-dose methyrapone stimulation test with the combination 250 microgram/dl cosyntropin stimulation test. However, the methyrapone stimulation is not frequently performed in practice due to limitation in availability of drug. Therefore, we selected a low dose cosyntropin (1 microgram) stimulation test for diagnosis of AI. It has been suggested that it might be more sensitive than the 250 microgram stimulation test[2,11,13].

Prevalence reports of AI in critically ill patients varied widely from 0% to 77%[2]. However, overall prevalence of AI in critically ill medical patients approximate 10% to 20%, with a rate as high as 60% in septic shock patients[12,13]. The recently published study by Kwon et al[15], which was undertook to evaluate the incidence of relative adrenal insufficiency [RAI], showed a 58% rate while the reports of Annane et al[7] was 77%. They both used a similar criteria as the present study. It is well established that AI was frequently observed in patients with septic shock. However, in the present study, AI was found in 46% of the cases. The authors observed the prevalence of AI was lower than other studies because there was a difference in the population of patients studied and the degree of severity illness.

We found that clinical features of fatigue, fever, hypotension, hypoglycemia, hyponatremia, hyperkalemia, and other laboratory results were not helpful to diagnose adrenal insufficiency. Corticosteroid insufficiency associated acute critically illness was difficult to recognize by clinical symptoms because these features were often masked by changes in fluid replacement[13,16]. Laboratory assessment of hyponatremia and hyperkalemia are uncommon because mineralocorticoid secretion remains intact. Other investigators demonstrated lower parentage of eosinophilia associated with low response to ACTH[17]. In the authors knowledge, the finding of hypotension, refractory to fluid therapy and requiring vasopressor were strongly associated with the presence of AI.

The present data demonstrate that usage of herbal medicine was an independent risk factors predicting AI. This could be important in rural Thailand where people frequently used herbal contaminated glucocorticoid component. The degree of suppression HPA axis depends on many factors including the glucocorticoid potency, the dosage, and duration of usage[12,13]. Others risk factors such as serum CO_2 less than 18 mEq/L and CHF were good independent predictors for patients suspicious AI in the ICU, especially in septic shock. This is because of the limitation of physical examination or non-specific symptoms and laboratory finding (as discussed above) that remained hemodynamic instability despite adequate fluid resuscitation. A recent study showed that the greater severity of disease and organ failure evaluated by the sequential organ failure assessment [SOFA] score and laboratory data such as low pH/bicarbonate and platelet count were independent predictor of RAI in critically-ill patients[18]. That study was retrospective and included patients who were receiving glucocorticoid, antifungal agents, and etomidate, which interfered with HPA axis. Kwon et al[15] did a prospective study that showed the SOFA score as an independent risk factor for RAI. SAP II score and arterial pH were protective independent risk factors, similar to the present study. They found that SAP II score and serum creatinine less than 2 mg/dl are independent risk factors that lower the occurring AI with septic shock.

The present study is the first report of the mortality in relationship to the baseline cortisol during septic shock in Thais. The patients with low cortisol (less than 25 microgram/dl) who are not treated with corticosteroids and patients with very high level (more than 45 microgram/dl) have high mortality[13,19-21]. Annane et al[9] reported a mean random cortisol level of 34 microgram/dl with septic shock, in non-survivors having higher level than survival (39 microgram/dl versus 28 microgram/dl). The authors use of threshold random cortisol cutoff at 25 microgram/dl for assessment of adequate cortisol response to critical illness. This is supported by the study of Zaloga et al[22]. The present results show the Kaplan-Meier curve of cumulative survival by comparing in septic shock patients who had a baseline cortisol of less than 25 microgram/dl had longer survival days than the group with baseline cortisol range greater than 25 microgram/dl (median survival time 21 days versus 12 days). The authors agreed with both studies of Marik et al[23] and Annane et al[9] that suggested high cortisol level associated with increased mortality. However, based on the results of the present study, it remains unclear whether the causes are from circulating mediator or direct effect of elevated cortisol concentration secreted during severe illness. The highest values in those with the highest illness-severity score associated with the

highest mortality[24,25].

The present study has several limitations. Most patients studied received different regimen of fluid replacement and type of vasopressor. The authors did not identify the type of herbal medicine and the duration of using, which may affect HPA axis or change in cortisol concentration after cosyntropin stimulation test. In addition, the authors realized in subgroup that received corticosteroid treatment with early shock reversal showed a longer survival time. The present study also measured the total cortisol not the unbound form cortisol or free cortisol, which is physiologically active and homeostatically more regulated than total cortisol. This is because of the common finding of hypoalbuminemia in septic shock[3,26].

Conclusion

The AI is common in Thai septic shock. Prevalence of AI is 46% and frequently unrecognized in critical illness during hospitalization. The low dose (1 microgram) cosyntropin stimulation test should be performed in patient with a history of herbal medicine used, serum CO_2 lower than 18 mEq/L, and CHF. The baseline cortisol level below 25 microgram/dl is associated with longer survival days.

What is already known on this topic?

1. AI was reported widely in critical illness and septic shock patients[2].

2. AI can be fatal in stress subjects and HPA dysfunction remains an under-diagnosed disorder in critical illness[13].

3. Investigation of HPA axis in critical illness have several complicated factors, the expected cortisol levels vary with severity of disease and both high and low cortisol levels have been shown to associate with poor prognosis[23].

4. There are no study of whether risk factors in septic shock can predict AI during admission including relationship between baseline cortisol and survival time.

What this study adds?

The present study has interesting findings. First, we find the helpful risk factors to predict AI in Thai septic shock are history of prior herbal medicine used, serum CO_2 of less than 18 mEq/L, and CHF. The second, the data clearly define that baseline cortisol less than 17.7 microgram/dl is a reliable cutoff to recognize corticosteroid insufficiency in critically ill and recommend to test ACTH stimulation testing. Finally, subgroup of septic shock with low baseline cortisol, especially less than 25 microgram/dl is associated with lower mortality.

Acknowledgement

The authors would like to thank the nursing staffs of the Division of Pulmonary and Tuberculosis, the staffs in Division of Clinical Chemistry and Clinical Pathology for their help in completing the study, to Amporn Iamtha for preparing the manuscript, and to Jayanton Patumanond for recommending the statistical analysis of the data.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Marik PE. Mechanisms and clinical consequences of critical illness associated adrenal insufficiency. Curr Opin Crit Care 2007;13:363-9.
2. 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.
3. Ho JT, Al Musalhi H, Chapman MJ, Quach T, Thomas PD, Bagley CJ, et al. Septic shock and sepsis: a comparison of total and free plasma cortisol levels. J Clin Endocrinol Metab 2006; 91:105-14.
4. Widmer IE, Puder JJ, Konig C, Pargger H, Zerkowski HR, Girard J, et al. Cortisol response in relation to the severity of stress and illness. J Clin Endocrinol Metab 2005;90:4579-86.
5. 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.
6. de Jong MF, Beishuizen A, van Schijndel RJ, Girbes AR, Groeneveld AB. Risk factors and outcome of changes in adrenal response to ACTH in the course of critical illness. J Intensive Care Med 2012;27:37-44.
7. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. Am J Respir Crit Care Med 2006;174:1319-26.

8. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008; 358:111-24.
9. Annane D, Sebille V, Charpentier C, Bollaert PE, Francois 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.
10. 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. Intensive Care Med 2013;39:165-228.
11. Abdu TA, Elhadd TA, Neary R, Clayton RN. Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 1999;84:838-43.
12. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881-93.
13. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. Chest 2002;122:1784-96.
14. Ratanarat R, Promsin P, Srivijitkamol A, Leemingsawat C, Permpikul C. Diagnosis of corticosteroid insufficiency in Thai patients with septic shock. J Med Assoc Thai 2010;93 Suppl 1: S187-95.
15. 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.
16. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med 1997;337:1285-92.
17. Beishuizen A, Vermes I, Hylkema BS, Haanen C. Relative eosinophilia and functional adrenal insufficiency in critically ill patients. Lancet 1999; 353:1675-6.
18. de Jong MF, Beishuizen A, Spijkstra JJ, Girbes AR, Strack van Schijndel RJ, Twisk JW, et al. Predicting a low cortisol response to adrenocorticotrophic hormone in the critically ill: a retrospective cohort study. Crit Care 2007;11:R61.
19. De Waele JJ, Hoste EA, Baert D, Hendrickx K, Rijckaert D, Thibo P, et al. Relative adrenal insufficiency in patients with severe acute pancreatitis. Intensive Care Med 2007;33: 1754-60.
20. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. Lancet 1991;337:582-3.
21. Bollaert PE, Fieux F, Charpentier C, Levy B. Baseline cortisol levels, cortisol response to corticotropin, and prognosis in late septic shock. Shock 2003;19:13-5.
22. Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency. Crit Care Clin 2001;17: 25-41.
23. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med 2003;31:141-5.
24. Moran JL, Chapman MJ, O'Fathartaigh MS, Peisach AR, Pannall PR, Leppard P. Hypocortisolaemia and adrenocortical responsiveness at onset of septic shock. Intensive Care Med 1994;20:489-95.
25. Schroeder S, Wichers M, Klingmuller D, Hofer M, Lehmann LE, von Spiegel T, et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. Crit Care Med 2001;29:310-6.
26. Hamrahian AH, Oseni TS, Arafah BM. Measurements of serum free cortisol in critically ill patients. N Engl J Med 2004;350:1629-38.