

Adrenal insufficiency during septic shock*

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Objective: To determine whether a baseline (random) cortisol concentration $<25 \mu\text{g/dL}$ in patients with septic shock was a better discriminator of adrenal insufficiency than the standard (250 μg) and the low-dose (1 μg) corticotropin stimulation tests as assessed by the hemodynamic response to steroid replacement.

Setting: Intensive care unit.

Patients: Fifty-nine patients with septic shock. Their mean age was 57 ± 16.7 yrs; 29 were male.

Interventions: A baseline cortisol concentration was obtained. Patients then received an intravenous injection of 1 μg of corticotropin (low-dose test) followed 60 mins later by an injection of 249 μg of corticotropin (high-dose test). Cortisol concentrations were obtained 30 and 60 mins after low- and high-dose corticotropin. All patients were administered hydrocortisone (100 mg every 8 hrs) for the first 24 hrs while awaiting results of cortisol assessment. Patients were considered steroid responsive if the pressor agent could be discontinued within 24 hrs of the first dose of hydrocortisone.

Measurements and Main Results: Forty-seven percent of patients died. Twenty-two percent of patients met the diagnostic criteria of adrenal insufficiency by the low-dose test and 8% by the high-dose test. However, 61% of patients met the criteria of

adrenal insufficiency when we used a baseline cortisol concentration of $<25 \mu\text{g/dL}$. Twenty-two patients (37%) were steroid responsive; the baseline serum cortisol was $14.1 \pm 5.2 \mu\text{g/dL}$ in the steroid-responsive patients compared with $33.3 \pm 18 \mu\text{g/dL}$ in the steroid-nonresponsive patients ($p < .0001$). Ninety-five percent of steroid-responsive patients had a baseline cortisol concentration $<25 \mu\text{g/dL}$. Fifty-four percent of steroid responders had a diagnostic low-dose test and 22% a diagnostic high-dose test. Receiver operating characteristic curve analysis revealed that a stress cortisol concentration of 23.7 $\mu\text{g/dL}$ was the most accurate diagnostic threshold for determination of the hemodynamic response to glucocorticoid therapy.

Conclusions: Adrenal insufficiency is common in patients with septic shock, the incidence depending largely on the diagnostic test and criteria used to make the diagnosis. There is clearly no absolute serum cortisol concentration that distinguishes an adequate from an insufficient adrenal response. However, we believe that a random cortisol concentration of $<25 \mu\text{g/dL}$ in a highly stressed patient is a useful diagnostic threshold for the diagnosis of adrenal insufficiency. (Crit Care Med 2003; 31:141–145)

KEY WORDS: sepsis; shock; adrenal insufficiency; cortisol; corticotropin; hypothalamic-pituitary-adrenal axis; endocrine; glucocorticoids

Infection is accompanied by activation of the hypothalamic-pituitary-adrenal axis. This activation is an essential component of the general adaptation to stress and the response to illness, and it is required for optimal recovery. Cortisol is an essential hormone required for normal function of all cells in the body. It is required for carbohydrate-protein-lipid metabolism, immune function, synthesis of catecholamines, adrenergic receptor synthesis and action, maintenance of vascular tone, and numerous other functions (1–3). The secretion of cortisol is regulated

via the central nervous system hypothalamic-pituitary-adrenal axis.

There is increasing evidence of reversible adrenal insufficiency in critically ill patients with sepsis (4–8). However, the incidence of adrenal insufficiency varies with the diagnostic test and concentration of cortisol used to diagnose the disorder (8). Traditionally, a serum cortisol concentration $>18 \mu\text{g/dL}$ has been regarded as a normal adrenal response to stress (9). This concentration is based primarily on the cortisol response to high-dose (HD) corticotropin in noncritically ill patients. Animal and human studies demonstrate increasing concentrations of catecholamines and cortisol with increasing severity of stress, with hypotension and sepsis being two of the most intense stressors (10, 11). In response to hypotension and following trauma or surgery, circulating cortisol concentrations almost always exceed 25 $\mu\text{g/dL}$ (6–9, 12–20). These stressors assess the response of the entire hypothalamic-pituitary-adrenal axis. However,

the traditional short HD corticotropin stimulation test (which uses 250 μg of corticotropin) stimulates the adrenal glands directly, bypassing the central nervous system-hypothalamic-pituitary components of the axis. The importance of this is highlighted by the fact that we have previously demonstrated that 88 of 124 critically ill patients had inappropriately low ($<40 \text{ pg/mL}$) adrenocorticotropic hormone (ACTH) concentrations (21). Furthermore, circulating corticotropin concentrations are 40–200 pg/mL during stress but may be as high as 60,000 pg/mL after HD corticotropin (5–7, 17, 20). These high concentrations of corticotropin can result in a normal cortisol response in patients who fail to respond to hypoglycemia or hypotension (8). Consequently, many investigators use the low-dose (LD) corticotropin stimulation test (1 μg of corticotropin) in unstressed patients because this produces corticotropin concentrations in the cir-

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cultation of 100 pg/mL, approximating the normal corticotropin response to stress. The LD test has been shown to be more sensitive for detecting adrenal insufficiency in patients with defects in the hypothalamic-pituitary-adrenal axis (15, 22–26).

The aim of this study was to evaluate the sensitivity of the LD and HD corticotropin stimulation tests in patients with septic shock by using a baseline (random) cortisol concentration of 25 µg/dL as the gold standard for the diagnosis of adrenal insufficiency. In addition, the sensitivity and specificity of these diagnostic criteria were determined by using the hemodynamic response to steroids as a marker of adrenal insufficiency.

METHODS

This study was conducted in the Medical Intensive Care Unit at Washington Hospital Center, Washington, DC. Because adrenal testing is routinely performed in the unit and carries no risk to the patient, the Institutional Review Board waived the need for informed consent. During the period March 1999 to May 2000, all adult patients admitted to the Medical Intensive Care Unit who met the Society of Critical Care Medicine/American College of Chest Physicians criteria for septic shock were eligible for enrollment into the study (27). Patients with HIV infection or a prior history of adrenal insufficiency and patients who received any dose of corticosteroids within the prior year were excluded (28–31). None of the patients received etomidate, ketoconazole, or other drugs known to suppress adrenal function. Patients were volume resuscitated with lactated Ringer's solution and a 6% hydroxyethyl starch solution (Hespan, DuPont, Wilmington, DE). Norepinephrine was the vasopressor agent of choice (32). Dopamine was not used. Dobutamine was used in patients with a pulmonary artery catheter who had a cardiac index $<3.5 \text{ L}\cdot\text{min}^{-1}\cdot\text{M}^{-2}$ (32).

Consecutive patients who met the inclusion criteria for septic shock underwent LD (1 µg) and HD (249 µg) corticotropin stimulation testing (Cosyntropin, Organon, West Orange, NJ) within 48 hrs of admission to the Medical Intensive Care Unit. All patients were on norepinephrine at the time of study. The tests were performed as follows: after a baseline serum cortisol concentration was drawn, the patient received 1 µg of corticotropin followed 60 mins later by 249 µg of corticotropin. Serum cortisol concentrations were drawn 30 and 60 mins (LD30 and LD60) after the 1-µg dose and 30 (90 mins from start) and 60 mins (120 mins from start) after the 249-µg dose (HD30 and HD60). In previous testing, we found that sequential LD-HD cor-

ticotropin testing produced a 30-min response to HD corticotropin that was similar to the response obtained when the HD test was repeated 1–2 days after the sequential test, indicating that priming of the cortisol response to LD corticotropin during LD testing does not occur in critically ill patients. After completion of the LD and HD corticotropin stimulation test, all patients were treated empirically with hydrocortisone 100 mg intravenously every 8 hrs. The cortisol results were available within 24 hrs of testing. Steroid responsiveness was defined as the cessation of the need for norepinephrine to maintain a mean arterial pressure of $>65 \text{ mm Hg}$ within 24 hrs of the first dose of hydrocortisone (33–35). Hydrocortisone was continued in patients with a baseline cortisol concentration of $<25 \text{ µg/dL}$ and in the steroid-responsive patients.

Data Collection and Analysis. The patients' demographic, clinical, and laboratory data were recorded in an electronic database (Access 2000, Microsoft, Redmond, WA). Summary statistics were compiled to allow a description of the patient population. The diagnostic sensitivity of the LD and HD test was determined by using a baseline cortisol concentration of 25 µg/dL as the reference method. In addition, the sensitivity and specificity of each test in predicting the hemodynamic response to corticosteroid treatment were determined. The stress (baseline) cortisol concentration that was the most accurate predictor of the hemodynamic response to corticosteroids was determined by receiver operating characteristic curve analysis. Statistical analysis was done with NCSS 2000 (Kaysville, UT). Chi-square analysis with Fisher's exact test (when appropriate) was used to compare categorical data. Continuous data were compared by using Student's *t*-test. Unless otherwise stated, all data are expressed as mean (SD) or percentages, with statistical significance declared for probability values of $\leq .05$.

RESULTS

Fifty-nine patients with septic shock were studied. Thirty were female and 29 were male. The average age of the patients was 57 ± 16.7 yrs. Twenty-eight patients (47%) died. The primary admitting diagnoses of the patients were as

follows: pneumonia 26, primary septicemia 14, urosepsis 7, abdominal sepsis 6, catheter-related sepsis 5, and acute endocarditis 1.

The baseline and postcorticotropin-stimulated cortisol concentrations for the entire cohort were as follows: baseline, 26.2 ± 17.4 ; LD30, 32.1 ± 18.1 ; LD60, 31.5 ± 7.6 ; HD30, 35.4 ± 19.0 and HD60, 38.7 ± 19.5 . The baseline cortisol was 20.9 ± 12.1 in the survivors and 31.9 ± 20.5 in the nonsurvivors ($p = .01$). Thirty-six patients (61%) had adrenal insufficiency when we used a baseline cortisol concentration of $<25 \text{ µg/dL}$ as the reference method (Table 1). When we used the standard diagnostic threshold (a postcorticotropin-stimulated cortisol of $<18 \text{ µg/dL}$), 13 (22%) patients had adrenal insufficiency by the LD test and five (8%) patients with the HD test. When we used a baseline cortisol of 25 µg/dL as the reference method, the LD test had a sensitivity of 62% whereas the HD test had a sensitivity of 24%.

All 59 patients with septic shock received hydrocortisone (100 mg intravenously every 8 hrs) for 24 hrs while awaiting the results of cortisol measurements. Of these patients, 22 patients (37%) were steroid responsive (cessation of norepinephrine within 24 hrs). The baseline serum cortisol was $14.1 \pm 5.2 \text{ µg/dL}$ in the steroid-responsive patients compared with $33.3 \pm 18 \text{ µg/dL}$ in the steroid-nonresponsive patients ($p < .0001$). Ninety-five percent of steroid-responsive patients had stress cortisol concentrations $<25 \text{ µg/dL}$. However, only 54% of steroid-responsive patients had a diagnostic LD test and 22% a diagnostic HD test. The specificities of the tests were 57%, 97%, and 100%, respectively. The area under the receiver operating characteristic curve of the stress (baseline) cortisol concentration was 0.84; a stress cortisol concentration of 23.7 µg/dL had the best discriminating power, with a sensitivity of 0.86, a specificity of 0.66, a likelihood ratio of 2.6, a positive

Table 1. Baseline and postcorticotropin-stimulated cortisol levels (µg/dL) after low-dose (LD) and high-dose (HD) tests (mean \pm SD) stratified by adrenal insufficiency (baseline cortisol, $<25 \text{ µg/dL}$)

Patients	Baseline	LD30	LD60	HD30	HD60
Adrenal insufficiency (n = 36) (61%)	15.8 \pm 5.3	21.2 \pm 7.6	21.6 \pm 8.5	24.6 \pm 8.8	28.0 \pm 10.5
Normal (n = 23)	42.3 \pm 17.4	48.9 \pm 16.9	47.2 \pm 16.9	52.4 \pm 18.5	55.6 \pm 18.5

LD30, 30 mins after low-dose corticotropin; LD60, 60 mins after low-dose corticotropin; HD30, 30 mins after high-dose corticotropin; HD60, 60 mins after high-dose corticotropin.

predictive value of 0.62, and a negative predictive value of 0.88.

The septic shock patients with adrenal insufficiency (baseline cortisol <25 µg/dL) could be divided into three groups based on the postcorticotropin-stimulated cortisol concentrations (Table 2). Group 1 (n = 15; 42%) consisted of patients with a low baseline cortisol concentration (<25 µg/dL) and failure to increase their cortisol above 25 µg/dL with both LD and HD corticotropin (primary adrenal failure). Group 2 patients (n = 10; 28%) had low baseline cortisol concentrations but increased their cortisol concentrations above 25 µg/dL with both LD and HD corticotropin (hypothalamic-pituitary failure). Group 3 (n = 11; 30%) had low baseline cortisol concentrations but failed to increase the concentration above 25 µg/dL with LD corticotropin. However, the cortisol concentration did increase above 25 µg/dL with HD corticotropin (ACTH resistance).

The clinical characteristics of the patients with septic shock grouped according to the presence or absence of adrenal insufficiency (using a baseline cortisol value of 25 µg/dL) are presented in Table 3. The serum glucose was significantly lower and the percentage of eosinophils significantly higher in patients with adrenal insufficiency. The groups did not differ with respect to baseline blood pressure or organ function (i.e., renal, hepatic, pulmonary failure).

DISCUSSION

This is the first report to evaluate both the LD and HD corticotropin stimulation test in patients with septic shock. The most important finding of this study is that the incidence of adrenal insufficiency in septic shock patients depends on the diagnostic test and criteria used to make the diagnosis. Twenty-two percent of patients met the diagnostic criteria of adrenal insufficiency by the LD test and 8% by the HD test. However, 61% of patients met the criteria of adrenal insufficiency when we used a baseline cortisol concentration of <25 µg/dL as the diagnostic threshold. The sensitivity of a baseline cortisol <25 µg/dL in predicting steroid responsiveness was 96%, compared with 54% for the LD test and 22% for the HD test. The baseline serum cortisol was 14.1 ± 5.2 µg/dL in the steroid-responsive patients compared with 33.3 ± 18 µg/dL in the steroid-nonresponsive patients. These data are similar to those

Table 2. Cortisol levels (µg/dL) in septic shock patients with adrenal insufficiency (baseline cortisol, <25 µg/dL) stratified by type of adrenal insufficiency

Patients	Baseline	LD30	LD60	HD30	HD60
Group 1 (n = 15)	12.1 ± 3.7	15.4 ± 4.0	15.2 ± 3.9	17.2 ± 4.3	18.9 ± 4.1
Group 2 (n = 10)	20.4 ± 3.5	31.1 ± 3.9	32.2 ± 6.1	34.7 ± 7.9	41.7 ± 7.5
Group 3 (n = 11)	16.1 ± 4.7	19.9 ± 3.8	19.9 ± 3.9	25.8 ± 2.0	27.9 ± 2.2

LD30, 30 mins after low-dose corticotropin; LD60, 60 mins after low-dose corticotropin; HD30, 30 mins after high-dose corticotropin; HD 60, 60 mins after high-dose corticotropin; Group 1, primary adrenal failure; group 2, hypothalamic-pituitary failure; group 3, adrenocorticotrophic hormone resistance.

Table 3. Clinical characteristics of septic shock patients with and without adrenal insufficiency (baseline cortisol <25 µg/mL)

Characteristic	HPA Insufficiency (n = 36)	Normal (n = 23)
Age, yrs	56 ± 15	59 ± 17
Sodium, mEq/L	140 ± 6.3	141 ± 7.5
Potassium, mEq/L	3.9 ± 0.6	4.2 ± 1.1
Blood urea nitrogen, mg/dL	33 ± 17	39 ± 12
Serum glucose, mg/dL	121 ± 31	183 ± 109 ^a
WBC, cells × 1000/mm ³)	12.1 ± 7.7	12.2 ± 8.2
Eosinophils, %	1.9 ± 1.2	0.3 ± 0.4 ^a

HPA, hypothalamic-pituitary-adrenal; WBC, white blood cells.
^ap < .005.

of Rivers et al. (33), who evaluated adrenal function in a group of vasopressor-dependent surgical patients. In a subgroup of patients treated with corticosteroids, the baseline serum cortisol was 49 µg/dL in the steroid nonresponders and 20 µg/dL in those patients who were weaned from vasopressors within 24 hrs of the initiation of steroid treatment. In the Rivers et al. study, one patient in the steroid-responsive group had a baseline serum cortisol >25 µg/dL and only two nonresponders had a baseline concentration <25 µg/dL (33). It should be noted that the diagnostic stress cortisol threshold of 25 µg/dL that was used in this study closely approximates the value of 23.7 µg/dL determined by receiver operating characteristic analysis. The hemodynamic response to steroids has been used as an end point in other studies that have evaluated the effect of corticosteroids on outcome in sepsis (34–37). Although the hemodynamic response to steroids may be a crude marker of acute adrenal insufficiency, we have no other end organ or biochemical marker to measure at this time. However, hypotension may be a useful surrogate marker of inadequate glucocorticoid activity during severe illness. Glucocorticoids are required for

normal reactivity to angiotensin II, epinephrine, and norepinephrine, contributing to the maintenance of vascular tone, cardiac contractility, and blood pressure (38, 39). Clearly, as demonstrated in our study, not all hypotensive patients with sepsis have adrenal insufficiency and will respond to stress doses of hydrocortisone. A number of other pathogenetic mechanisms may be responsible for the vasodilation and resistance to vasopressor agents found in septic patients, including increased release of nitric oxide, activation of potassium ATP ion channels in arterioles, and inappropriately low vasopressin concentrations (40–43). Furthermore, other therapeutic interventions may restore arterial tone in steroid-responsive patients.

An interesting aspect of this study is the finding that septic patients with adrenal insufficiency could be divided into three groups based on their response to LD and HD corticotropin. Fifteen patients (42%) with adrenal insufficiency failed to respond to both LD and HD corticotropin and most likely represent patients with primary adrenal gland failure. Ten patients (28%) responded to both LD and HD corticotropin. We postulate that these patients lack adequate

secretion of corticotropin-releasing hormone or corticotropin and represent patients with secondary adrenal insufficiency. In a previous study we demonstrated that 85% of the patients with adrenal insufficiency (baseline cortisol of $<25 \mu\text{g/dL}$) had inappropriately low ($<40 \text{ pg/mL}$) ACTH concentrations (21). A third group of patients (30%) failed to respond to LD corticotropin but responded normally to HD corticotropin. Due to the ability of pharmacologic doses of corticotropin to produce a normal response when physiologic stress levels of corticotropin were ineffective, we postulate that this group represents patients with corticotropin resistance. Resistance may result from the production of circulating antagonists or from receptor/postreceptor resistance. This is the first report of ACTH resistance in patients with sepsis. Further study is needed to better define the pathophysiologic alterations involved in these different groups.

Annane et al. (44) and other investigators have used an absolute increase in cortisol ($\Delta \text{ max}$) of $<9 \mu\text{g/dL}$ following an HD test to be diagnostic of "occult adrenal insufficiency." (44). We believe this concept to be seriously flawed (45, 46). The change in cortisol concentration following cosyntropin stimulation ($\Delta \text{ max}$) is a measure of adrenal reserve and not adrenal function. A highly stressed patient with a baseline serum cortisol of $40 \mu\text{g/dL}$ and a $\Delta \text{ max}$ of $6 \mu\text{g/dL}$ clearly does not have adrenal insufficiency. The Δ cortisol must be interpreted in the context of the baseline cortisol concentration.

It is noteworthy that the mean baseline serum cortisol concentration in the 36 patients with septic shock and adrenal insufficiency (baseline concentration $<25 \mu\text{g/mL}$) was $15.8 \pm 5.3 \mu\text{g/mL}$. This concentration is similar to that of unstressed healthy volunteers (12). The most convincing evidence of reversible adrenal failure during sepsis comes from the study of Briegel and colleagues (4), who performed an HD test in 20 patients during septic shock and repeated the test after recovery. Thirteen of the 20 patients had adrenal insufficiency as defined by a baseline cortisol concentration of $<25 \mu\text{g/dL}$. Remarkably, in these 13 patients, the basal and postcorticotropin-stimulated cortisol concentrations were higher after recovery than during the episode of septic shock.

The cause of adrenal insufficiency in patients with septic shock is multifactorial

(8, 46). Complete destruction of the adrenal glands by infection or hemorrhage (i.e., coagulopathy) is uncommon. Inhibition of steroid synthesis by drugs such as etomidate or ketoconazole is also uncommon and did not occur in any of our patients. The most likely mechanisms include decreased synthesis and/or release of corticotropin-releasing hormone, corticotropin, and cortisol by cytokines and other circulating mediators released during sepsis. Plasma from patients with sepsis has been demonstrated to impair the synthesis of corticosteroids (47–49). Tumor necrosis factor- α impairs corticotropin-releasing hormone stimulated corticotropin release and cortisol synthesis (50–53). Corticostatin, a defensin peptide released by infection, possesses anticorticotropin activity (54, 55).

Our data suggest that hypotensive septic patients with a baseline cortisol concentration $<25 \mu\text{g/dL}$ are likely to respond to stress doses of corticosteroids. However, patients in septic shock with a baseline cortisol concentration $>25 \mu\text{g/dL}$ may also respond to corticosteroids. These patients may have a decreased number of glucocorticoid receptors, decreased affinity of the receptor for its ligand, or postreceptor abnormalities (13, 49, 56, 57). Reduced activity of glucocorticoid enzymes during endotoxemia despite elevated circulating glucocorticoid concentrations provides evidence to support impaired intracellular actions of glucocorticoids during sepsis (58). We therefore suggest that random cortisol be measured in all patients in septic shock, followed by the administration of stress doses of hydrocortisone (100 mg intravenously every 8 hrs). The hydrocortisone should be continued in those patients with a random cortisol concentration $<25 \mu\text{g/dL}$ and in all hemodynamic responders.

This study was not designed to evaluate the benefits/risks of glucocorticoid treatment of patients with septic shock. Previous studies using short-term pharmacologic doses of corticosteroids failed to find benefit from treatment of patients with septic shock (59, 60). However, recent studies using stress doses of corticosteroids (i.e., 300 mg of hydrocortisone over 24 hrs) over longer periods of time (1–2 wks) have reported a more rapid clinical improvement and reduced mortality rate in the steroid-treated patients (34–37).

CONCLUSION

Adrenal insufficiency is common in patients with septic shock, the incidence depending largely on the diagnostic test and criteria used to make the diagnosis. There is clearly no absolute serum cortisol concentration that distinguishes an adequate from an insufficient adrenal response. However, we believe that a random cortisol concentration of $<25 \mu\text{g/dL}$ in a highly stressed patient is a useful diagnostic threshold for the diagnosis of adrenal insufficiency.

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