Adrenal function in sepsis: The retrospective Corticus cohort study

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Objective: **To refine the value of baseline and adrenocorticotropin hormone (ACTH)-stimulated cortisol levels in relation to mortality from severe sepsis or septic shock.**

Design: **Retrospective multicenter cohort study.**

Setting: **Twenty European intensive care units.**

Patients: **Patients included 477 patients with severe sepsis and septic shock who had undergone an ACTH stimulation test on the day of the onset of severe sepsis.**

Interventions: **None.**

Measurements and Main Results: **Compared with survivors, nonsurvivors had higher baseline cortisol levels (29.5 ± 33.5 vs. 24.3 ± 16.5 μg/dL, $p = .03$) but similar peak cortisol values (37.6 ± 40.2 vs. 35.2 ± 22.9 μg/dL, $p = .42$). Thus, nonsurvivors had lower Δmax (i.e., peak cortisol minus baseline cortisol) (6.4 ± 22.6 vs. 10.9 ± 12.9 μg/dL, $p = .006$). Patients with either baseline cortisol levels <15 μg/dL or a Δmax ≤9 μg/dL had a likelihood ratio of dying of 1.26 (95% confidence interval, 1.11–1.44), a longer duration of shock, and a shorter survival time. Patients with a Δmax ≤9 μg/dL but any baseline cortisol value had a likelihood ratio of dying of 1.38 (95% confidence interval, 1.18–1.61).**

Conclusions: **Although delta cortisol and not basal cortisol level was associated with clinical outcome, further studies are still needed to optimize the diagnosis of adrenal insufficiency in critical illness. Etomidate influenced ACTH test results and was associated with a worse outcome. (Crit Care Med 2007; 35:1012–1018)**

KEY WORDS: severe sepsis; septic shock; adrenocorticotropin hormone test; cortisol; mortality; adrenal insufficiency

Adrenal insufficiency is a frequent finding in patients with severe sepsis and carries prognostic implications (1, 2). Patients with septic shock who failed to increase their cortisol above 9 μg/dL following an intravenous bolus of 250 μg of adrenocorticotropin hormone (ACTH) were less likely to respond to vasopressors (3) and more likely to die (2). In these patients, replacement therapy with corticosteroids (i.e., 200–300 mg of hydrocortisone or equivalent per day) improved survival without causing overt harm (4, 5).

In unstressed subjects, adrenal insufficiency is confirmed when the baseline cortisol is <3 μg/dL or 250 μg ACTH-stimulated cortisol is <18–20 μg/dL (6, 7). In critical illness it has been proposed that a diagnosis of adrenal insufficiency is likely when a random cortisol level is <15 μg/dL and/or the increment after ACTH is ≤9 μg/dL (8). Other definitions are based on a cortisol increment after ACTH of ≤9 μg/dL, regardless of basal cortisol levels (9), or are based on a random cortisol level of ≤25 and ≤20 μg/dL in hypotensive and normotensive patients, respectively (10). In patients with severe hypoproteinemia, adrenal insufficiency may be best defined by a baseline serum free cortisol concentration ≤2.0 μg/dL or ACTH-stimulated free cortisol concentrations ≤3.1 μg/dL (11). Most of these definitions have been developed based on data collected from relatively small patient populations. The objective of this multicenter retrospective study was to gather data from a large cohort of patients with severe sepsis to further refine the value of baseline and ACTH-stimulated cortisol levels.

METHODS

This was a retrospective study performed on data collected from patients in 20 European intensive care units (ICU) as part of the Corticus project (12). Data from 77% of the patient population were extracted from databases of previously published studies, whereas the remainder came from patients admitted to participating sites before the start of the prospective, interventional limb of the Corticus study (i.e., a randomized controlled trial of hydrocortisone vs. placebo for septic shock) (4, 5). The study protocol was approved at the internal review boards from each participating center, with a waiver, as it was a retrospective analysis of databases.

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Study Population

All patients who had undergone an intravenous ACTH stimulation test within the 24 hrs following the onset of sepsis and who met criteria for severe sepsis or septic shock (adapted from the American College of Chest Physicians/Society of Critical Care Medicine consensus conference) (13) were included in the study (Appendix).

Septic shock was defined as severe sepsis and the need for vasopressors to maintain a systolic blood pressure >90 mm Hg.

Exclusion criteria were pregnancy, age <18 yrs, underlying major disease other than sepsis and life expectancy <2 months, immunosuppression, chemotherapy or radiation therapy within 4 wks before the study, human immunodeficiency virus (HIV) infection, cardiopulmonary resuscitation within 72 hrs before study commencement, advanced directive to withhold or withdraw life-sustaining treatment (i.e., do-not-resuscitate order), administration of any glucocorticoids within the last month, or administration of etomidate within 24 hrs before the study.

Data Collection

Clinical Evaluation. At the onset of severe sepsis, the following variables were recorded: a) general characteristics including age and gender, date of ICU admission, diagnosis, category of admission (medical or surgical); b) severity of illness as assessed by the Simplified Acute Physiology Score (SAPS) II (14) and vital signs (body temperature, systolic blood pressure, heart rate); and c) interventions (which were left to the physician's judgment and recorded as per the patient's chart) including volume of fluid infusion administered per 24 hrs, antibiotics, type and titration of vasopressors, corticosteroid therapy, need for mechanical ventilation, and surgical procedures.

Laboratory Variables. At the onset of severe sepsis, blood cultures and cultures of other potential sites of infection were obtained. Hematology and blood chemistry data, arterial lactate, and blood gas determinations were recorded. A short adrenocorticotropin stimulation test was performed with 0.25 mg of tetracosactrin given intravenously. Blood samples were taken immediately before the test (T0) and 30 (T30) or 60 (T60) minutes afterward. The cortisol response (Δmax) was defined as the difference between T0 and the highest of the T30 and T60 concentrations.

Definitions

Prospective definitions developed by expert intensivists and endocrinologists were used:

Absolute adrenal insufficiency: basal cortisol level <7.3 μg/dL (200 nmol/L)

Relative adrenal insufficiency (suspicion): basal cortisol level between 7.3 and 25.4 μg/dL (200–700 nmol/L).

The following definitions for adrenal insufficiency were also evaluated:

Baseline cortisol level ≤25 μg/dL (700 nmol/L) (10)

Baseline cortisol levels <15 μg/dL (413 nmol/L) or delta cortisol ≤9 μg/dL (248 nmol/L) (8)

Delta cortisol ≤9 μg/dL regardless of baseline cortisol values (2, 4, 9)

Statistical Analysis

Statistical analyses were conducted using the Systat 10.0 software package (Systat, Chicago, IL). The prognostic values for the probability of dying for patient characteristics collected at the onset of severe sepsis or septic shock, and of the short ACTH test results, were investigated. Univariate analyses were performed in which the data were compared between survivors and nonsurvivors using Student's *t*-test for continuous variables and chi-square test for categorical variables (or Fisher's exact test as appropriate). Correlations were tested using Spearman's rank-correlation test. Outcomes were assessed by the Kaplan-Meier method and compared between groups with the log-rank test for all variables. Stepwise multivariate analyses were performed using a logistic regression model to estimate the odds ratio (OR) of dying (plus 95% confidence intervals, CI) at hospital. A p value of ≤.15 was used to enter variables into the model. Calibration of the logistic model was assessed using the Hosmer-Lemeshow goodness-of-fit test to evaluate the importance of the discrepancy between observed and expected in-hospital mortality. Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve to evaluate how well the model distinguished patients who lived from those who died. Iterative stepwise and backward selection procedures were used to select the variables that were significantly related to death, as assessed by the likelihood ratio test. Finally, we computed likelihood ratios of dying with corresponding 95% CIs for diagnostic tests based on the various proposed definitions of adrenal insufficiency (described previously) (15). For all tests, $p < .05$ was considered statistically significant. Data are expressed as mean ± SD or median, interquartile range (IQR), and range.

RESULTS

A total of 562 patients were evaluated. Eighty-five patients were excluded because they were HIV positive (37 patients), had received corticosteroids (16 patients) or other immunosuppressive therapy (20 patients) within the last month, had cardiopulmonary resuscitation within the 72 hrs before study (eight patients), were <18 yrs old (two patients), or had incomplete data for the ACTH test (two patients). This left 477 patients who could be evaluated.

Study Population Characteristics

Demographic characteristics, primary reasons for ICU admission, severity of illness score, and vital signs are shown in Table 1. There were 442 (93%) mechanically ventilated patients and 253 (53%) septic shock patients at the time of inclusion. Two hundred and ten (44%) patients received corticosteroids for the treatment of septic shock, 135 at the time of inclusion and 75 subsequently. Two hundred and thirty-seven (50%) patients received at least one dose of etomidate >24 hrs before inclusion into the study.

The lung was the main source of infection, and Gram-positive organisms were the most frequent cause of infection. Eighty-one (17%) patients had positive blood cultures (Table 2).

The in-hospital crude mortality was 286 of 477(60%, 95% CI, 55–65%) with a median time to death of 7 days (IQR, 2–18). Among the 253 patients receiving vasopressors at baseline, the median time to vasopressor withdrawal was 5 days (IQR, 3–7). For the 191 survivors, medians for ICU and hospital length of stay were 23 days (IQR, 11–43) and 38 days (IQR, 24–60), respectively.

ACTH Test and Adrenal Function

Results from the ACTH test are shown in Table 3. The absolute cortisol increment between T30 and T0 was significantly lower than between T60 and T0 (4.6 ± 17.4 μg/dL vs. 6.6 ± 19.9 μg/dL, $p = .007$, n = 429). One hundred and forty-one patients (33%) had a greater cortisol increment between T30 and T0 than between T60 and T0. Thus, 20 of 477 patients (4%) would be adjudged as nonresponders to ACTH by using only the T60 value for cortisol and responders by using the maximum increment in cortisol between T30 and T60. The prevalence of adrenal insufficiency according to the various definitions is given in Table 4. There was a fairly large variation in the prevalence of adrenal insufficiency depending on whether it was solely based on baseline cortisol levels, on the cortisol increment after ACTH, or on the combination of both data.

Table 1. Patients' main characteristics

Variables	Whole Population (n = 477) Mean (SD) or % (No.)	95% Confidence Interval
Age, yrs	61 (16)	59–62
Gender, male	65 (308)	59–69
Reasons for ICU admission		
Septic shock	23 (109)	18–29
Severe sepsis	20 (94)	15–25
ALI/ARDS	33 (155)	27–39
Trauma	4 (19)	2–7
CNS dysfunction	10 (49)	7–15
Nonseptic shock	4 (20)	2–7
Acute renal failure	3 (14)	1–6
Postoperative	2 (8)	0–4
Acute pancreatitis	1 (7)	0–4
Mesenteric ischemia	0.4 (2)	0–2
SAPS II	59 (22)	57–61
Temperature, °C	37.9 (1.8)	37.7–38.1
Systolic blood pressure, mm Hg	92 (23)	90–94
Heart rate, beats/min	114 (23)	112–116
Lactate, mmol/L	4.3 (3.8)	3.8–4.8

ICU, intensive care unit; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CNS, central nervous system; SAPS, Simplified Acute Physiology Score.

Age, SAPS II, temperature, systolic blood pressure, heart rate, and lactate are given as mean (SD). The other variables are given as % (n).

Table 2. Main characteristics of the septic episodes

Variables	Whole Population (n = 477) % (No.)	95% Confidence Interval
Source		
Lung	43 (206)	37–49
Abdominal	17 (83)	13–23
Primary septicemia	16 (75)	11–21
Soft tissues	10 (46)	6–14
Urogenital	6 (29)	3–10
CNS	3 (12)	1–5
Other	4 (17)	2–6
None	2 (9)	1–4
At least one positive blood culture	17 (81)	12–24
Pathogen		
Pure Gram-negative infection	34 (160)	28–40
Pure Gram-positive infection	36 (170)	30–42
Mixed	12 (59)	9–17
Fungal	2 (11)	1–5
Parasitic	0.4 (2)	0–2
Viral	0.4 (2)	0–2
No organism isolated	15 (73)	1–20

CNS, central nervous system.

Baseline cortisol and Δmax cortisol were positively correlated ($r^2 = .26$, $p < .001$) (Fig. 1). There was no correlation between age or SAPS II and baseline ($p = .15$ and $p = .05$, respectively) or peak ($p = .11$ and $p = .23$, respectively) cortisol levels, or Δmax ($p = .64$ and $p = .29$, respectively). We found no difference in cortisol levels or in Δmax for different sources of infection ($p = .09$ and $p = .82$, respectively) or for different types of pathogens ($p = .76$ and $p = .17$, respectively). There was no significant difference between patients with severe sepsis or septic shock regarding baseline (29.5 ± 36.1 vs. 25.3 ± 18.1 μg/dL, $p = .10$) or peak cortisol levels (37.2 ± 47.6 vs. 36.1 ± 24.9, $p = .73$). By contrast, Δmax was significantly greater in severe sepsis than in septic shock (10.9 ± 14.3 vs. 5.4 ± 23.7 pg/dL, $p = .002$). In septic shock, no correlation was seen between the time in shock before inclusion and either baseline ($p = .99$) or peak ($p = .62$) cortisol levels, or Δmax ($p = .43$).

ACTH Test and Outcome

Analyses performed in the subset of 267 patients who did not receive corticosteroids were very similar to those obtained in the whole population. Therefore, only data for the whole population are reported.

Mortality

Comparisons in cortisol levels between survivors and nonsurvivors are shown in Table 3. Mortality was not significantly different between basal cortisol quartiles, whereas the lower the Δmax quartile, the greater the mortality ($p < .001$) (Fig. 2). In the 267 patients who did not receive corticosteroids, three had a baseline cortisol level of ≤3 μg/dL, and all died. In the 240 etomidate-free patients, cortisol levels were not different between nonsurvivors and survivors (29.3 ± 41.2 vs. 24.0 ± 17.5, $p = .17$), whereas Δmax was significantly lower (5.4 ± 24.1 vs. 12.1 ± 14.5, $p = .007$). In the 237 etomidate-treated patients, nonsurvivors had lower cortisol levels than survivors (24.5 ± 15.7 vs. 29.2 ± 21.4, $p = .05$) and lower Δmax values (7.6 ± 5.7 vs. 10.5 ± 2.4, $p = .04$).

Analysis of ROC curves showed that cortisol levels at T0, T30, or T60 or peak cortisol levels were not associated with death, in contrast to T30–T0, T60–T0, or Δmax values (Fig. 3). In addition, areas under the ROC curves were significantly higher for T30–T0, T60–T0, or Δmax than for T0, T30, T60, and peak cortisol levels (Table 5). Table 4 shows that when baseline cortisol level was <15 μg/dL or Δmax ≤9 μg/dL, the likelihood ratio of dying was 1.26 (95% CI, 1.11–1.44). A Δmax value ≤9 μg/dL had a likelihood ratio of dying of 1.38 (95% CI, 1.18–1.61). Multivariate regression analysis showed that the need for vasopressors was a strong predictor of death (OR, 105.83; 95% CI, 25.06–446.95), whereas the use of corticosteroids was associated with a strong reduction in the risk of dying (OR, 0.21; 95% CI, 0.08–0.52) (Table 6). The Hosmer-Lemeshow goodness-of-fit test showed that the model was well calibrated with $p = .59$ (a large p value indicating that there is no large discrepancy between observed and expected mortality). The area under the ROC curve was 0.899, showing that the model discriminated well between patients who lived and those who died.

Time to Death

The median time to death was not significantly different between patients with cortisol levels above and below 7.3 μg/dL (log-rank $p = .39$), between patients with levels in or outside the range 7.3–25 μg/dL (log-rank $p = .35$), or between patients with cortisol levels above or below 25 μg/dL (log-rank $p = 0.20$). However, nonresponders to the ACTH test had a shorter time to death than responders, 19 vs. 87 days (log-rank $p < .001$). Similarly, patients with a baseline cortisol level <15 μg/dL or Δmax ≤9

Table 3. Adrenocorticotropin hormone test results according to in-hospital mortality

Variables	Whole Population (n = 477)	Survivors (n = 191)	Nonsurvivors (n = 286)	*p* Value
Cortisol at T0	27.3 ± 28.1	24.3 ± 16.5	29.5 ± 16.5	.03
Cortisol at T30	31.8 ± 28.1	31.6 ± 22.0	31.9 ± 31.4	.93
Cortisol at T60	33.9 ± 28.4	33.9 ± 21.5	33.9 ± 32.3	.98
Peak cortisol	36.6 ± 34.3	35.2 ± 22.9	37.6 ± 40.2	.42
T30–T0	4.6 ± 17.4	7.3 ± 11.0	2.8 ± 20.4	.003
T60–T0	6.6 ± 19.9	9.6 ± 12.3	4.7 ± 23.5	.003
Δmax	8.2 ± 19.4	10.9 ± 12.9	6.4 ± 22.6	.006

T0, immediately before the test; T30, 30 mins after the test; T60, 60 mins afterward; Δmax, peak cortisol minus baseline cortisol.

All values are given as μg/dL.

Table 4. Prevalence of adrenal insufficiency according to the various definitions and associated prognostic value in 477 patients with severe sepsis and septic shock

	Whole Population (n = 477) No. (%)	Survivors (n = 191) No. (%)	Nonsurvivors (n = 286) No. (%)	Likelihood Ratio of Death	95% Confidence Interval
Baseline cortisol, μg/dL					
<7.3[a]	46 (10)	21 (11)	25 (9)	0.80	0.55–1.16
7.3 ≤ and <25[b]	243 (51)	99 (52)	144 (50)	0.97	0.81–1.16
≥25	188 (39)	71 (37)	117 (41)	1.10	0.87–1.39
Baseline cortisol, <15 or ≥ Δmax ≤9, μg/dL					
Yes	338 (71)	117 (61)	221 (77)	1.26	1.11–1.44
No	139 (29)	74 (39)	65 (23)	0.59	0.44–0.78
Delta cortisol ≤9, μg/dL					
Yes	303 (64)	99 (52)	204 (71)	1.38	1.18–1.61
No	174 (36)	92 (48)	82 (29)	0.60	0.47–0.75

Δmax, peak cortisol minus baseline cortisol.

[a]Absolute adrenal insufficiency; [b]relative adrenal insufficiency.

μg/dL also had a reduced time to death, namely 23 vs. 87 days (log-rank $p = .001$).

Time to Shock Reversal

The median time to shock reversal was not significantly different between patients with cortisol levels above or below 7.3 μg/dL (log-rank $p = .32$), between patients with levels in or outside the range 7.3–25 μg/dL (log-rank $p = .28$), between patients with levels above or below 25 μg/dL (log-rank $p = .19$), or between nonresponders and responders to ACTH (log-rank $p = .13$). Patients with a baseline cortisol level <15 μg/dL or Δmax ≤9 μg/dL had a longer time on vasopressors (log-rank $p = .05$).

DISCUSSION

This is the largest cohort study to date investigating adrenal function in patients with severe sepsis and septic shock. The high SAPS II scores, the large proportion of patients receiving vasopressors and/or mechanical ventilation, and the high mortality rate underline the severity of illness in this population.

The current study confirmed that the proportion of patients with adrenal dysfunction varied from 10% to 71% according to various definitions proposed in the literature (2,8–10,16) and that nonsurvivors had higher baseline cortisol levels and a lower cortisol response to corticotropin (2, 9).

This study, however, also provides new information. First, we found that very few patients are mistakenly classified as nonresponders when using a 60-min ACTH-stimulated cortisol level instead of the maximum value between the 30- and 60-min levels. In addition, areas under the ROC curves were not different for T60–T0, T30–T0, and Δmax, suggesting that the sampling at T30 may not provide any benefit in terms of diagnostic accuracy. Thus, sampling 30 mins after ACTH injection is not routinely required in septic patients, and the test can be just performed with baseline and 60-min ACTH-stimulated levels. Second, neither age,

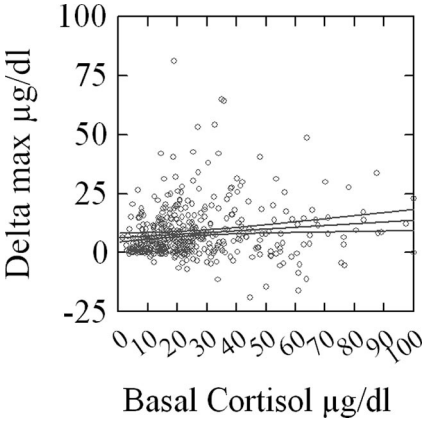

Figure 1. Baseline cortisol levels and cortisol response to corticotropin in all patients (n = 477). Plots of baseline cortisol levels (x-axis) vs. absolute cortisol increment after 250 μg of adrenocorticotropin hormone (y-axis) in 477 patients with severe sepsis or septic shock. Lines indicate regression line and 95% confidence intervals, showing a positive correlation between basal cortisol and cortisol response (Δmax) ($r^2 = .26$, $p < .001$). The equation for the linear regression is Δmax = 23.71 + 0.21·baseline cortisol. The F ratio from the analysis of variance was 7.43 ($p = .07$), indicating that the hypothesis that the slope of the regression line is 0 could be rejected.

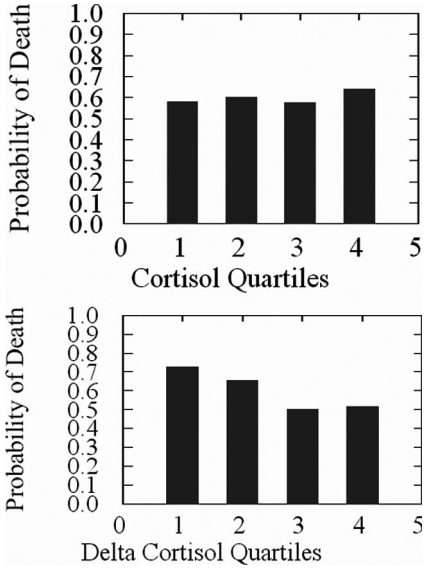

Figure 2. Probability of death according to baseline cortisol levels quartiles (*top*) and cortisol response (Δmax) quartiles (*bottom*). Mortality was not significantly different between basal cortisol quartiles, whereas the lower Δmax quartiles had a higher mortality than those with higher increments ($p < .001$).

SAPS II, the source of infection, nor the type of causative pathogen influenced the results of the ACTH test. The presence of shock was significantly associated with a blunted cortisol response to ACTH. However, the duration of shock before the

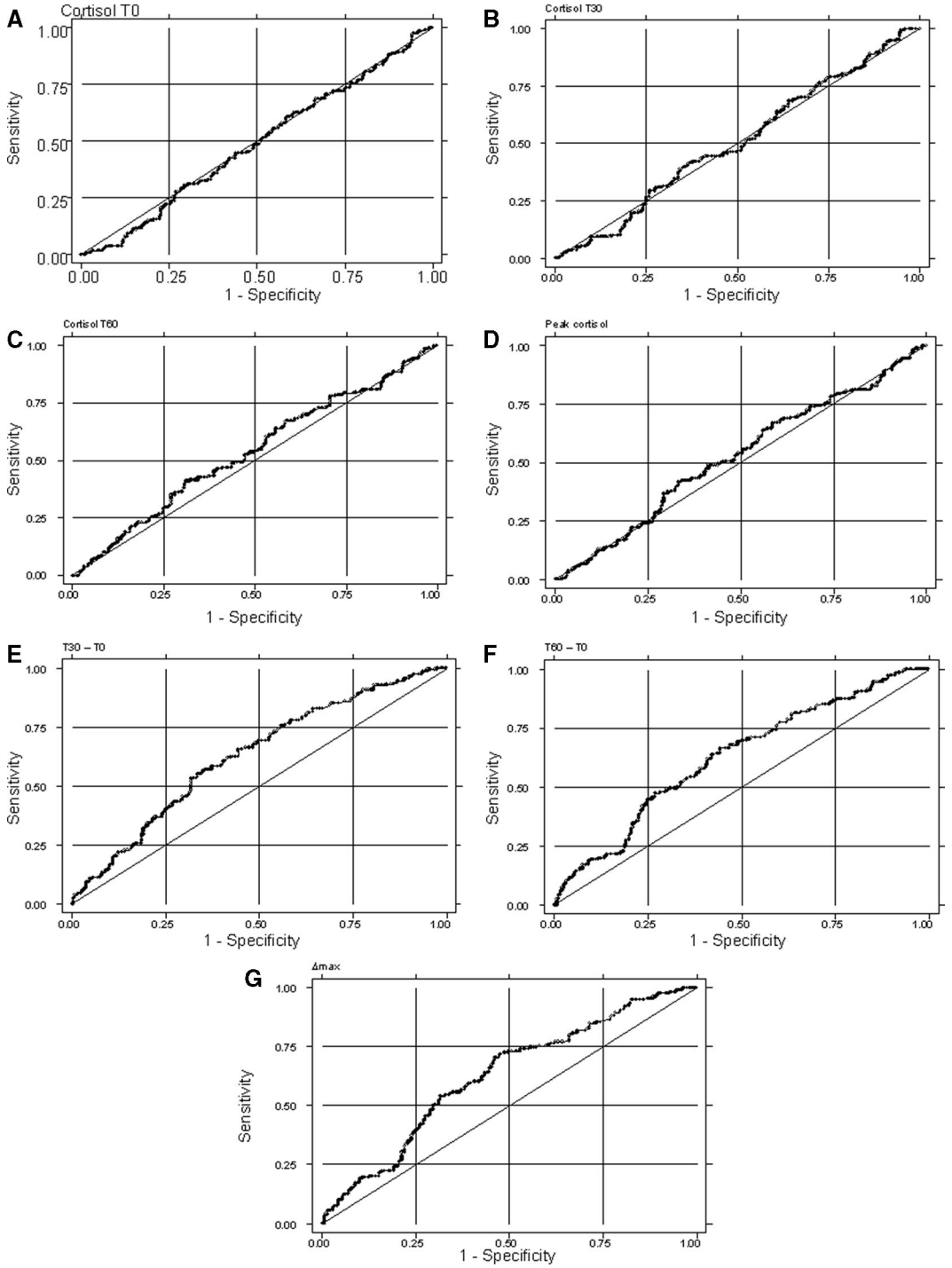

Figure 3. Receiver operating characteristic curves for cortisol levels at time zero (T0), 30 mins (T30), 60 mins (T60), peak cortisol, T30–T0, T60–T0, and cortisol response (Δmax).

ACTH test did not influence its results. Third, this study showed that baseline cortisol levels and Δmax were positively correlated. This may argue against the concept of exhaustion of the adrenal glands during sepsis. This finding is in keeping with the previous finding that adrenocortical cells are up-regulated in response to excessive stimulation (17). Finally, this was the first study that investigated the value of the definition of adrenal insufficiency during critical illness as proposed by Cooper and Stewart (8), that is, baseline cortisol levels <15 μg/dL or Δmax ≤ 9 μg/dL. Among the patients who did not receive steroids for severe sepsis or septic shock, all three patients with cortisol levels ≤ 3 μg/dL died. As reported for unstressed patients (6), a cortisol level ≤ 3 μg/dL in patients with severe sepsis or septic shock may indicate definite adrenal insufficiency. Otherwise, cortisol levels alone, regardless of the cutoff value, are not independent predictors of shock reversal, survival duration, or hospital mortality. Nonresponders to ACTH, or the group of pa-

Table 5. Areas under receiver operating characteristic (ROC) curves for in-hospital mortality in 477 severe sepsis and septic shock patients

Variables	Areas Under ROC Curves, mean ± SD	95% Confidence Intervals
Cortisol at T0	0.48 ± 0.03	0.43–0.54
Cortisol at T30	0.52 ± 0.03	0.46–0.57
Cortisol at T60	0.54 ± 0.03	0.48–0.59
Peak cortisol	0.52 ± 0.03	0.47–0.58
T30–T0	0.63 ± 0.03[a,b,c,d]	0.57–0.68
T60–T0	0.62 ± 0.03[a,b,c,d]	0.57–0.68
Δmax	0.62 ± 0.02[a,b,c,d]	0.57–0.69

T0, immediately before the test; T30, 30 mins after the test; T60, 60 mins afterward; Δmax, peak cortisol minus baseline cortisol.

[a]$p < .05$ for comparisons with area of T0 levels; [b]$p < .05$ for comparisons with area of T30 levels; [c]$p < .05$ for comparisons with area of T60 levels; [d]$p < .05$ for comparisons with area of peak levels. All values are given as μg/dL.

Table 6. Predictors of hospital mortality in 477 patients with septic shock

Variables	Univariate Analysis OR	Univariate Analysis 95% CI	Multivariate Analysis OR	Multivariate Analysis 95% CI
Age, yrs	1.02	1.01–1.04	1.02	1.00–1.05
Gender, male	0.99	0.82–1.20	—	—
SAPS II	1.05	1.04–1.06	1.01	0.98–1.03
Systolic blood pressure, mm Hg	0.99	0.98–0.99	0.99	0.96–1.02
Diastolic blood pressure, mm Hg	0.98	0.97–0.99	1.01	0.96–1.05
Heart rate, beats/min	1.00	0.99–1.01	—	—
Arterial lactate, mmol/L	1.11	1.01–1.22	0.96	0.84–1.11
Cortisol, μg/dL				
T0	1.01	1.00–1.02	1.01	0.99–1.04
T30	1.00	0.99–1.01	—	—
T60	1.00	0.99–1.01	—	—
Peak cortisol	1.00	0.99–1.01	—	—
Δmax	0.98	0.96–0.99	0.96	0.90–0.99
Adrenal insufficiency, yes[a]	1.16	0.87–1.55	—	—
T0 <15 or Δmax ≤9, yes	2.15	1.44–3.21	4.19	0.61–28.88
Δmax ≤9, yes	2.31	1.58–3.39	1.56	0.26–9.42
Mechanical ventilation, yes	1.21	0.85–1.70	—	—
Vasopressors, yes	38.52	20.69–71.73	105.83	25.06–446.95
Etomidate, yes	1.53	1.06–2.26	1.82	0.52–6.36
Corticosteroids, yes	0.55	0.38–0.80	0.21	0.08–0.52

OR, odds ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score; T0, immediately before the test; T30, 30 mins afterward; T60, 60 mins afterward; Δmax, peak cortisol minus baseline cortisol.

[a]Three categories: cortisol <7.3 μg/dL (absolute adrenal insufficiency); cortisol between 7.3 and 25 μg/dL (relative adrenal insufficiency); cortisol >25 μg/dL (normal adrenal function).

tients with baseline cortisol levels <15 μg/dL or Δmax ≤9 μg/dL, had a longer duration of shock and a shorter survival time. Moreover, the Δmax (*per se*) was independently associated with in-hospital death; that is, the lower the delta cortisol the higher the risk of death. Thus, in severe sepsis and septic shock, one may also recognize adrenal insufficiency by Δmax ≤9 μg/dL (2, 3, 9) or by baseline cortisol levels <15 μg/dL or Δmax ≤9 μg/dL (8). However, the rather low areas under the ROC curves suggested that further investigations are required to optimize the definition of adrenal insufficiency in severe sepsis.

In this study, some patients were included who did receive etomidate >24 hrs before the ACTH test. Treatment with etomidate was associated with an increased risk of dying, particularly in patients who did not receive steroids. This finding is in keeping with the observed increased mortality in multiple trauma patients sedated with etomidate (18). This observation underlines that even a short course of etomidate may have a sustained unfavorable impact on survival from critical illness and strongly suggests that it should not be used in patients with severe sepsis (19).

Study Limitations

Although this study was retrospective, it was based on data prospectively gathered in the context of clinical trials. About half of these patients had a baseline cortisol level ≤20 μg/dL, and about one third had levels <15 μg/dL. These relatively low baseline levels of total cortisol may have resulted from low levels of albumin and cortisol binding globulin (11), levels of which were not available in this retrospective study. Nevertheless, because exogenous ACTH injection has no effect on albumin or cortisol-binding globulin levels, the increment in total cortisol following ACTH may directly reflect the increment in cortisol synthesis. In addition, in a recent study that used the overnight short metyrapone test to assess the integrity of the hypothalamic-pituitary-adrenal axis, no evidence for a difference in diagnostic accuracy was found between total and free cortisol levels (20). Thus, one may use the delta cortisol (ACTH-stimulated minus basal total cortisol) as an index of cortisol synthesis in the critically ill awaiting generalization of routine measurements of free cortisol.

The current study confirmed the prognostic value of the standard high-dose ACTH test in septic shock, which can be done using only baseline and T60 values. Although delta cortisol and not basal cortisol level was associated with clinical outcome, further studies are still needed to optimize the diagnosis of adrenal insufficiency in critical illness. Finally, physicians should be aware that etomidate influenced ACTH test results and clinical outcome.

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APPENDIX

Eligibility Criteria

Patients who met all following criteria for severe sepsis were included:

1. Clinical evidence of infection within the previous 72 hrs with either a) presence of neutrophils in a normally sterile body fluid; b) positive culture or Gram-negative stain of blood, sputum, urine, or normally sterile body fluid or space; or c) focus on infection (e.g., ruptured bowel with the presence of free air or bowel contents in the abdomen found at the time of surgery, wound with purulent drainage)
2. Evidence of systemic inflammatory response syndrome as defined by the presence of three or more of the following: a) pyrexia (body temperature $>38.0°C$ [$>100.4°F$]) or hypothermia (body temperature $<36.0°C$ [96.8°F]); b) tachycardia (heart rate >90 beats/min); c) tachypnea (respiratory rate >20 breaths/min or $Paco_2$ <32 mm Hg) or need for mechanical ventilation; or d) leukocytosis ($>12{,}000$ mm^3), leukopenia (<4000 mm^3), or $>10\%$ immature (band) forms
3. Evidence of hypotension, hypoperfusion, or organ system failure attributable to sepsis (not to underlying diseases) within the previous 24 hrs, including one of the following: a) Pao_2 <75 mm Hg or Pao_2/Fio_2 <250 in the absence of pneumonia); b) systolic blood pressure <90 mm Hg or reduction of >40 mm Hg from baseline; c) pH ≤ 7.3 or a base deficit >5.0 mmol/L, or lactate >2 mmol/L; d) urine output ≤ 0.5 mL/kg/hr for >1 hr and adequate fluid resuscitation; e) platelet count $\leq 100{,}000$/mm^3; f) $>20\%$ increase in prothrombin time or a $>20\%$ increase in partial thromboplastin time; and g) Glasgow Coma Scale score <14 and no sedation or acute change from baseline in behavior or cognitive function.