A 3-Level Prognostic Classification in Septic Shock Based on Cortisol Levels and Cortisol Response to Corticotropin

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Context The hypothalamic-pituitary-adrenal axis is a major determinant of the host response to stress. The relationship between its activation and patient outcome is not known.

Objective To evaluate the prognostic value of cortisol levels and a short corticotropin stimulation test in patients with septic shock.

Design and Setting Prospective inception cohort study conducted between October 1991 and September 1995 in 2 teaching hospital adult intensive care units in France.

Participants A total of 189 consecutive patients who met clinical criteria for septic shock.

Intervention A short corticotropin stimulation test was performed in all patients by intravenously injecting 0.25 mg of tetracosactrin; blood samples were taken immediately before the test (T0) and 30 (T30) and 60 (T60) minutes afterward.

Main Outcome Measures Twenty-eight–day mortality as a function of variables collected at the onset of septic shock, including cortisol levels before the corticotropin test and the cortisol response to corticotropin (Δmax, defined as the difference between T0 and the highest value between T30 and T60).

Results The 28-day mortality was 58% (95% confidence interval [CI], 51%-65%) and median time to death was 17 days (95% CI, 14-27 days). In multivariate analysis, independent predictors of death (P<.001 for all) were McCabe score greater than 0, organ system failure score greater than 2, arterial lactate level greater than 2.8 mmol/L, ratio of PaO2 to fraction of inspired oxygen no more than 160 mm Hg, cortisol level at T0 greater than 34 µg/dL and Δmax no more than 9 µg/dL. Three groups of patient prognoses were identified: good (cortisol level at T0 ≤34 µg/dL and Δmax >9 µg/dL; 28-day mortality rate, 26%), intermediate (cortisol level at T0 34 µg/dL and Δmax ≤9 µg/dL or cortisol level at T0 >34 µg/dL and Δmax >9 µg/dL; 28-day mortality rate, 67%), and poor (cortisol level at T0 >34 µg/dL and Δmax ≤9 µg/dL; 28-day mortality rate, 82%).

Conclusion Our data suggest that a short corticotropin test has a good prognostic value and could be helpful in identifying patients with septic shock at high risk for death.

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nonsurvivors compared with survivors.9-21 For this reason, in severe sepsis, the evaluation of the appropriate-ness of the activation of the HPA axis requires dynamic testing. In this re-spect, the most commonly used test is the short corticotropin stimulation test, normal adrenal function being defined by a plasma cortisol level (before or at 30 or 60 minutes after the injection of corticotropin) above 20 μg/dL.22 However, basal plasma cortisol levels are commonly greater than 20 μg/dL in se-vere sepsis and the use of the absolute increase in plasma cortisol levels after the intravenous injection of corticotropin may be more useful to evaluate ad-renal function.12,13 Indeed, occult adrenal insufficiency (ie, an absolute increment of cortisol concentrations <9 μg/dL) after corticotropin may be associ-ated with impaired pressor responsivness to norepinephrine23 and a high morta lity rate.24,25 Such results must be confirmed since other investigators have not found any relationship between cort-isol response to corticotropin and sur-vival from sepsis.20

In the context of renewed interest in corticosteroids as therapy for septic shock,14,15,21,23-25,27-30 we undertook a pro-spective study to determine the inci-dence of occult adrenal insufficiency in septic shock patients and to assess the factors associated with mortality, tak-ing special interest in cortisol levels and cortisol response to corticotropin.

METHODS

Study Population
All consecutive patients hospitalized in the ICU of 2 teaching hospitals (Ray-mond Poincaré hospital, Garches, France, and Antoine Béclère hospital, Clamart, France) between October 1991 and September 1995 were prospec-tively enrolled in the study if they met the follow-ing criteria for septic shock31:

(1) For less than 7 days, a systemic in-flammatory response as defined by 2 or more of the following: temperature higher than 38.5°C or lower than 35.0°C, heart rate of more than 90/min, respira-tory rate of more than 20/min or PaCO₂ of less than 32 mm Hg or need for me-

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well the model distinguished patients who lived from those who died. A Cox proportional hazards regression model was used to assess variables related to death. This model assumes that the effect of a variable on the instantaneous death rate is constant over time. This assumption was checked for all predictor variables entered in the model. Stepwise and backward selection procedures were used for both regression models (logistic and Cox) to iteratively select the variables that were significantly related to death, as assessed by the likelihood ratio test. For all tests, \( P < .05 \) was considered statistically significant.

### RESULTS

#### Patient Characteristics

Among the 189 patients admitted during the study period, 96 (51%) were recruited in the Garches center and 93 (49%) in the Clamart center. Of the 189 patients, 109 (58%; 95% CI, 51%-65%) died within the 28-day period following the onset of septic shock, 3 patients died after 28 days (they died after 31, 62, and 66 days, respectively). TABLE 1 shows patient characteristics at the onset of septic shock and results of the univariate analysis between the survivor and nonsurvivor groups. The McCabe and OSF scores and the Simplified Acute Physiology Score II were significantly associated with mortality. Among clinical and biological factors, mean arterial pressure, platelet count, arterial lactate and pH, the ratio of the PaO\(_2\) to the fraction of inspired oxygen (FiO\(_2\)) were significantly different between survivors and nonsurvivors. Compared with survivors, nonsurvivors had significantly higher basal plasma cortisol levels (T\(_0\)) and lower cortisol response to corticotropin (\( \Delta \text{max} \)). The mean maximum [SD] doses of dobutamine during the first 6 hours following the onset of septic shock were significantly lower in survivors compared with nonsurvivors (8.6 [4.5] vs 11.6 [6.4] \( \mu \)g/kg per minute; \( P = .005 \)). Treatment with hydrocortisone during the follow-up was also less frequent in survivors compared with nonsurvivors (12% vs 29%; \( P = .006 \)). The number of patients who had documented infection, sites of infection, and strains diagnosed at the onset of septic shock are shown in TABLE 2. Sites of infection were similar among survivors and nonsurvivors whereas gram-positive microorganisms were more common among nonsurvivors and gram-negative microorganisms were more common among survivors (\( P = .008 \)).

All variables found to be significantly different between the survivor and nonsurvivor groups, according to the univariate analysis performed on patient characteristics at the onset of septic shock (apart from physician's interventions, namely the administration of catecholamines or hydrocortisone), were entered into the logistic regression model. Among those variables, the following 5 remained independently associated with death: McCabe and OSF scores, arterial lactate, PaO\(_2\)/FiO\(_2\), and \( \Delta \text{max} \) (TABLE 3). Increases in the McCabe and OSF scores were associated with the highest odds of dying with 2.95 (95% CI, 1.56-5.59) and 2.41 (95% CI, 1.51-3.84), respectively. The Hosmer-Lemeshow goodness-of-fit test showed that the model was well calibrated with \( P = .44 \) (a large \( P \) value indicating that there is not a large discrepancy between observed and expected mortality). The area under the ROC curve was 0.863, showing that the model discriminated well between patients who lived and those who died.

### Survival

The median time to death was 17 days (95% CI, 14-27 days) for all patients.
Univariate analysis was performed to compare survival time distributions of all variables collected at the onset of septic shock using the log-rank test. Variables associated with death were McCabe score of more than 0 \((P = .005)\), OSF score greater than 2 \((P < .001)\), Simplified Acute Physiology Score II greater than 55 \((P < .001)\), mean arterial pressure of 60 mm Hg or less \((P < .001)\), arterial lactate level greater than 2.8 mmol/L \((P < .001)\), arterial pH of 7.33 or less \((P < .001)\), PaO₂/FIO₂ of 160 mm Hg or less \((P = .002)\), T0 greater than 26 µg/dL \((P = .003)\), and Δmax of 8 µg/dL or less \((P < .001)\). Among variables related to physician interventions, higher doses for dopamine \((P = .04)\) and treatment with hydrocortisone \((P = .04)\) were significantly associated with death.

Variables identified by the univariate analysis with the log-rank test (apart from physician interventions) were entered in the Cox proportional hazards regression model to identify the variables that have an important effect on mortality. As shown in Table 3, 6 variables were selected as being independently associated with mortality: McCabe score of more than 0, OSF score greater than 2, arterial lactate level greater than 2.8 mmol/L, PaO₂/FIO₂ of 160 mm Hg or less, T0 greater than 26 µg/dL, and Δmax of 8 µg/dL or less.

**Cortisol Levels and Cortisol Response to Corticotropin**

We further investigated the prognostic value of the short corticotropin test using univariate analyses (with χ², log-rank tests, and ROC curves) and multivariate analyses (with logistic and Cox models). The 2 variables, T0 and Δmax, were first studied separately. The values of T0 and Δmax were discretized according to their 25th, 50th, and 75th percentiles as well as to their mean value. The reference value of 9 µg/dL for Δmax was added for Δmax.

As shown in Table 4, values of T0 larger than 34 µg/dL (mean) or even 45 µg/dL (75th percentile) were significantly associated with death rates and distribution of survival times, with the smallest \(P\) value (χ² and log-rank tests) for 34 µg/dL. With T0 greater than 26 µg/dL (50th percentile), the difference in the proportion of deaths was almost significant (χ² test) whereas the difference in the distributions of survival times was significant (log-rank test). All the threshold values of T0 are displayed on the ROC curve (Figure 1). The area under the ROC curve was 0.620 and the highest value reached for sensitivity and specificity, which is usually close to the intersection point between the ROC curve and the second bisecting line, was the threshold value of 26 µg/dL, which

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was associated with a sensitivity of 0.554 and a specificity of 0.584.

As shown in Table 4, all threshold values chosen for Δmax were significantly associated with death rates and distribution of survival times, with the smallest $P$ value ($\chi^2$ and log-rank tests) for $9 \mu g/dL$ (reference value). Using this threshold, the estimate of the incidence of occult adrenal insufficiency is 54% (95% CI, 47%-61%) in our septic shock patients. All the threshold values of Δmax are displayed on the ROC curve (Figure 1). The area under the ROC curve was 0.686 and the highest value reached for sensitivity and specificity was the reference value $9 \mu g/dL$, which was associated with a sensitivity of 0.679 and a specificity of 0.649.

The highest values of the $\chi^2$ and log-rank statistics were reached for $34 \mu g/dL$ for T0 whereas the highest values for sensitivity and specificity were reached for $26 \mu g/dL$. For Δmax, all results ($\chi^2$ and log-rank tests, and ROC curve) were in close agreement, leading to the same choice for the threshold value, namely $9 \mu g/dL$. Therefore, the following combinations of T0 and Δmax were studied: (1) T0 of 26 or $34 \mu g/dL$ or less and Δmax greater than $9 \mu g/dL$; (2) T0 of 26 or $34 \mu g/dL$ or less and Δmax of $9 \mu g/dL$ or less or a T0 greater than 26 or $34 \mu g/dL$ and Δmax greater than $9 \mu g/dL$; (3) T0 greater than 26 or $34 \mu g/dL$ and Δmax of $9 \mu g/dL$ or less. The information provided by T0 and Δmax together, for both threshold values of T0 (26 and $34 \mu g/dL$), was significantly associated with death rates and distribution of survival times (Table 5). However, the value of $34 \mu g/dL$ seems to be a more informative cut-off value than $26 \mu g/dL$. By using this threshold value, compared with $26 \mu g/dL$, the proportion of survivors was a bit higher (70% vs 68%) for combination 1 and the proportion of survivors was a bit lower (18% vs 20%) for combination 3. Moreover, the highest values of the $\chi^2$ and log-rank statistics were both reached with $34 \mu g/dL$. Using this threshold, the likelihood ratios for survival were 3.42 for T0 of $34 \mu g/dL$ or less and Δmax greater than $9 \mu g/dL$ and 0.31 for T0 greater than $34 \mu g/dL$ and Δmax of $9 \mu g/dL$ or less.

We included, in a multivariate logistic regression model, T0 and Δmax which were respectively discretized according to their mean and reference values ($34 \mu g/dL$ for T0 and $9 \mu g/dL$ for Δmax), the combination of T0 and Δmax, as well as the variables previously identified by the univariate analysis (Table 1). As shown in Table 6, high McCabe and OSF scores, high arterial lactate, low PaO2:FIO2, T0 greater than $34 \mu g/dL$, and Δmax of $9 \mu g/dL$ or less remained independently and significantly associated with death. The Hosmer-Lemeshow goodness-of-fit test showed that the model was well calibrated with $P = .75$. The area under the ROC curve was 0.884, showing that the model discriminated well between patients who lived and those who died.

We also used Cox proportional hazards regression model by adding T0, Δmax, and their combination in the same manner as previously described to

### Table 4. $\chi^2$ and Log-Rank Tests for Death Rates and Distribution of Survival Times for Different Values of Cortisol Levels Before Test and of Maximum Variation After Test

<table>
<thead>
<tr>
<th>Threshold Values (Percentile or Other)</th>
<th>Plasma Level, $\mu g/dL$</th>
<th>Total (N = 189)</th>
<th>Survivors (n = 77)</th>
<th>Nonsurvivors (n = 112)</th>
<th>Death Rates</th>
<th>Survival Times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2$</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Cortisol Level Before Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>25</td>
<td>$&gt;17$</td>
<td>141 (75)</td>
<td>53 (60)</td>
<td>88 (79)</td>
<td>2.3</td>
<td>.13</td>
</tr>
<tr>
<td>50</td>
<td>$&gt;26$</td>
<td>94 (50)</td>
<td>32 (42)</td>
<td>62 (55)</td>
<td>3.5</td>
<td>.06</td>
</tr>
<tr>
<td>Mean</td>
<td>$&gt;34$</td>
<td>63 (33)</td>
<td>16 (21)</td>
<td>47 (42)</td>
<td>9.2</td>
<td>.002</td>
</tr>
<tr>
<td>75</td>
<td>$&gt;45$</td>
<td>48 (25)</td>
<td>12 (16)</td>
<td>36 (32)</td>
<td>6.6</td>
<td>.01</td>
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<tr>
<td>Maximum Variation After Test</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>$&gt;2$</td>
<td>140 (74)</td>
<td>65 (84)</td>
<td>75 (67)</td>
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<td>.007</td>
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<td>50</td>
<td>$&gt;8$</td>
<td>94 (50)</td>
<td>51 (66)</td>
<td>43 (38)</td>
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<td>.001</td>
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<tr>
<td>Reference value</td>
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<td>50 (65)</td>
<td>36 (32)</td>
<td>19.8</td>
<td>.001</td>
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<tr>
<td>Mean</td>
<td>$&gt;11$</td>
<td>78 (41)</td>
<td>42 (56)</td>
<td>36 (32)</td>
<td>9.4</td>
<td>.002</td>
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<tr>
<td>75</td>
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<td>47 (25)</td>
<td>12 (16)</td>
<td>36 (32)</td>
<td>16.5</td>
<td>.001</td>
</tr>
</tbody>
</table>

*To convert values for cortisol to nanomoles per liter, multiply by 27.6.
the variables found to be significant in the univariate analysis to identify the variables that could have an important relationship with mortality. This time, the stepwise and backward selection procedures gave slightly different results. As shown in Table 7, the stepwise selection procedure identified the following variables as being independently associated with mortality: McCabe score of more than 0, OSF score greater than 2, arterial lactate level of more than 2.8 mmol/L, PaO2:FIO2 of 160 mm Hg or less, arterial pH of 7.33 or less, arterial pressure of 60 mm Hg or less, and T0 greater than 34 µg/dL, and Δmax of 9 µg/dL or less. The backward selection procedure gave slightly different results and identified the following variables as being independently associated with mortality: McCabe score of more than 0, OSF score greater than 2, mean arterial pressure of 60 mm Hg or less, arterial pH of 7.33 or less, PaO2:FIO2 of 160 mm Hg or less, T0 greater than 34 µg/dL, and Δmax of 9 µg/dL or less.

Figure 2 shows the survival curves for T0 (≤ or >34 µg/dL), Δmax (≤ or >9 µg/dL), and the combination of T0 and Δmax (T0 ≤34 µg/dL and Δmax >9 µg/dL; T0 >34 µg/dL and Δmax ≤9 µg/dL; or T0 >34 µg/dL and Δmax >9 µg/dL). A total of 109 deceased patients instead of 112 are taken into account in this figure because, as previously mentioned, 3 patients died after 28 days. Death occurred more rapidly for patients with T0 greater than 34 µg/dL (median time to death, 6 days [95% CI, 4-12 days]), Δmax of 9 µg/dL or less (median time of maximum variation after test of 9 µg/dL or less). A total of 109 deceased patients instead of 112 are taken into account in this figure because, as previously mentioned, 3 patients died after 28 days. Death occurred more rapidly for patients with T0 greater than 34 µg/dL (median time to death, 6 days [95% CI, 4-12 days]), Δmax of 9 µg/dL or less (median time of maximum variation after test of 9 µg/dL or less).
to death, 11 days [95% CI, 8-15 days]), and for the following combination of T0 and Δmax, a T0 greater than 34 µg/dL and Δmax of 9 µg/dL or less (median time to death, 5 days [95% CI, 2-12 days]). Three different survival patterns appear in Figure 2: (1) high (T0 ≤34 µg/dL and Δmax >9 µg/dL; 28-day mortality rate of 26%); (2) intermediate (T0 ≤34 µg/dL and Δmax ≤9 µg/dL or T0 >34 µg/dL and Δmax >9 µg/dL; 28-day mortality rate of 67%); and (3) low (T0 >34 µg/dL and Δmax ≤9 µg/dL; 28-day mortality rate of 82%).

**COMMENT**

In this study, we included ICU patients with well-defined diagnosis of septic shock, complete clinical and physiological data, and a complete follow-up. The study was mainly designed to assess, at the early course of septic shock, the incidence and the prognostic value of occult adrenal insufficiency.

The 28-day mortality from septic shock was 58% (95% CI, 51%-65%). This result is consistent with the 56% rate of ICU mortality at 28 days recently reported.1 In our patients with septic shock, the incidence of occult adrenal insufficiency was 54% (95% CI, 47%-61%).

Several factors have been suspected to be associated with mortality in severe sepsis and septic shock. The main prognostic factors reported to date are age, severity of patient's underlying disease, number of organ system dysfunctions, severity of illness scores, hypothermia, neutropenia, thrombocytopenia, lactic acidosis, multisource of infection, positive blood culture, type of infecting organism, blood concentrations of endotoxin, and cytokines. Since the initial reports of Waterhouse and Friderichsen, the implication and prognostic value of a secretory failure of the adrenal glands in patients with severe sepsis is still under debate.

In the 189 patients with septic shock included in our study, most of the foregoing factors were significantly associated with mortality in the univariate analyses. High basal plasma cortisol levels and weak cortisol response to corticotropin were also associated with mortality. After multivariate analyses, only 6 factors remained independently associated with death: ultimately or rapidly fatal underlying disease, more than 2 OSFs, arterial lactate level greater than 2.8 mmol/L, PaO2:FIO2 below 160 mm Hg, basal plasma cortisol levels above 34 µg/dL, and cortisol response to cor-

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**Figure 2. Survival Curves of Patients According to Basal Plasma Cortisol Levels (T0 ≤ or >34 µg/dL), Maximum Variation of Plasma Cortisol Between T0 and 30 and 60 Minutes After Corticotropin Test (Δmax ≤ or >9 µg/dL), and the Combination of T0 and Δmax**

Top, 62 of the 126 patients with T0 of 34 µg/dL or less died compared with 47 of the 63 with T0 of more than 34 µg/dL; P < .001 (log-rank test). Middle, 75 of the 103 patients with Δmax of 9 µg/dL or less died compared with 34 of the 86 patients with Δmax of more than 9 µg/dL; P < .001 (log-rank test). Bottom, 15 of the 57 patients with T0 of 34 µg/dL or less and Δmax of more than 9 µg/dL died compared with 66 of the 98 patients with T0 of 34 µg/dL or less and Δmax of more than 9 µg/dL; P < .001 (log-rank test). To convert values for cortisol to nanomoles per liter, multiply by 27.6.
corticotropic below 9 µg/dL. Thus, our study suggests that basal plasma cortisol levels are higher in the patients who have the highest risk of mortality, 1,7,10,16-18 with 34 µg/dL as the best cut-off point to discriminate between survivors and non-survivors from septic shock. One third of patients with septic shock had a basal cortisol level above 34 µg/dL. This study also shows that the weaker the cortisol response the higher the risk of death. 10,24,25 A difference of 9 µg/dL between basal cortisol levels and the highest of the 30- and 60-minute concentrations after corticotropin was the best cut-off point to discriminate between survivors and non-survivors from septic shock. More than 50% of patients with septic shock had a blunted cortisol response (Δmax ≤ 9 µg/dL) or a basal cortisol level above 34 µg/dL) allowed us to define 3 different patterns of activation of the HPA axis in septic shock. These patterns were clearly associated with 3 different outcomes. First, 30% of our patients with septic shock had what we consider to be adequate HPA axis activation with a basal cortisol level below 34 µg/dL and a cortisol response to corticotropin above 9 µg/dL. These patients had the lowest risk of death and a median survival time of more than 28 days. Second, almost 20% of our patients with septic shock had a basal cortisol level above 34 µg/dL with an occult adrenal insufficiency (Δmax ≤ 9 µg/dL). These patients had the highest risk of death and a median survival time of 5 days. Finally, more than 50% of our patients with septic shock had a basal cortisol level below 34 µg/dL and a cortisol response to corticotropin below 9 µg/dL or a basal cortisol level above 34 µg/dL and a cortisol response to corticotropin above 9 µg/dL. These patients had an intermediate risk of death and a median survival time of 12 days.

Thus, at onset of septic shock, basal plasma cortisol values and cortisol response to corticotropin appear as independent predictors of 28-day mortality, which allows us to propose a new prognostic classification of 3 groups. This 3-level classification only requires a short corticotropin test and has a good prognostic value. It should therefore be helpful in identifying a group of patients at high risk of death and in planning new randomized trials, particularly to evaluate the effectiveness of corticosteroids.

REFERENCES