Cortisol levels and mortality in severe sepsis

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Summary

OBJECTIVE Serum cortisol levels rise in response to the stress of critical illness but the optimal range of serum cortisol in such settings is not clearly defined. The objectives of this study were to determine the range of serum cortisol levels in a group of medical intensive care unit patients with severe sepsis/septic shock using uniform criteria, and to correlate serum cortisol levels to mortality.

DESIGN AND PATIENTS In a prospective observational fashion, 100 medical intensive care unit patients at Northwestern Memorial Hospital in Chicago were enrolled within 48 h of developing severe sepsis/septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine.

MEASUREMENTS A serum cortisol level was measured during the morning hours in the first 48 h of developing severe sepsis/septic shock. The severity of critical illness was measured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

RESULTS The average patient age was 63 ± 17 years, 54 patients were men. The average APACHE II score for all patients was 23 ± 7. In-hospital and 90-day mortality were 51% and 60%, respectively. Four patient groups were defined a priori based on morning serum cortisol levels and their in-hospital mortalities were as follows: group 1 (cortisol ≤ 345 nmol/l), n = 11, mortality 54%; group 2 (cortisol 345–552 nmol/l), n = 19, mortality 53%; group 3 (cortisol 552–1242 nmol/l), n = 54, mortality 41%; and group 4 (cortisol ≥ 1242 nmol/l), n = 16, mortality 81% (P < 0.01).

CONCLUSIONS Cortisol levels were elevated in most patients with septic shock. Cortisol levels less than 552 nmol/l occurred in 30% of patients with septic shock but the mortality in these patients was not significantly increased. Serum cortisol levels ≥ 1242 nmol/l were associated with significantly higher mortality.

Activation of the hypothalamic–pituitary–adrenal (HPA) axis has been well demonstrated in a number of physiologic stressful conditions such as burns (Lephart et al., 1987), surgery (Swan et al., 1957; Rivers et al., 2001), sepsis (Bouachour et al., 1995; Sibbald et al., 1977; Schein et al., 1990; Rothwell et al., 1991) and critical illness (Jarek et al., 1993). This response is necessary for regulation of homeostasis and survival (Munck et al., 1984; Lamberts et al., 1997). Glucocorticoids are important for maintenance of vascular tone, endothelial integrity, cardiac contractility and potentiation of catecholamine actions (Besse & Bass, 1966; Kalsner, 1969; Iversen and Salt, 1970).

It is generally accepted that cortisol levels are elevated under conditions of stress such as critical illness and severe sepsis/septic shock; however, the reported range of serum cortisol in such circumstances has varied widely (Sibbald et al., 1977; Finlay and McKee, 1982; Jurney et al., 1987; Schein et al., 1990; Rothwell et al., 1991; Span et al., 1992; Jarek et al., 1993; Bouachour et al., 1995; Soni et al., 1995; Annane et al., 2002). This variability may be secondary to enrolment of subjects with different degrees of stress. Recently, the concept of relative adrenal insufficiency (AI) in septic shock has been introduced. Patients with relative AI may have a suboptimal adrenal response to sepsis and may benefit from treatment with exogenous glucocorticoids (Bollaert et al., 1998; Briegel et al., 1999; Annane et al., 2002).

Unfortunately, the methods and criteria to diagnose AI or relative AI in critical illness/septic shock have not been well defined or standardized. Investigators have used a lack of increment of cortisol in response to corticotrophin (ACTH; Rothwell et al., 1991; Bouachour et al., 1995; Soni et al., 1995), or an inappropriate low cortisol level during critical illness/septic shock (Finlay & McKee, 1982; Zaloga & Marik, 2001), or both (Sibbald et al., 1977; Annane et al., 2000) to diagnose AI. Additionally, the lower end of serum cortisol used to diagnose AI in critical illness has ranged from less than 345 nmol/l to 690 nmol/l (Finlay & McKee, 1982; Bouachour et al., 1995; Annane et al., 2000; Rivers et al., 2001; Zaloga & Marik, 2001; Cooper & Stewart,
The aims of the present study were to determine the range of serum cortisol levels in a group of medical intensive care unit (MICU) patients with severe sepsis/septic shock using uniform criteria, and to correlate serum cortisol levels with mortality. Our objective was to identify cut-off levels for serum cortisol below or above which mortality in severe sepsis/septic shock might be adversely affected.

Patients and methods

Patient population

In this prospective, observational study, 100 septic patients from the MICU of Northwestern Memorial Hospital in Chicago were recruited between January 2001 and March 2002. The study was approved by the Institutional Review Board of Northwestern University. Study subjects were identified for recruitment by daily chart review performed by the primary investigators. Patients were enrolled if they fulfilled the criteria for sepsis induced acute dysfunction of at least one organ or system (severe sepsis) or septic shock (severe sepsis requiring vasopressor support). Sepsis was defined as three or more signs of systemic inflammatory response syndrome (SIRS; temperature \( \geq 38 \degree C \) or \( \leq 36 \degree C \), heart rate \( \geq 90 \), respiratory rate \( \geq 20 \) or partial pressure of arterial CO\(_2\) \( \leq 32 \) mmHg, white blood cell count \( \geq 12,000/\)µl or \( \leq 4000/\)µl or > 10% immature neutrophils) and known or suspected infection (Anonymous, 1992). Additionally, patients were only included in the study if the managing team had requested a serum cortisol level within the first 48 h of severe sepsis/septic shock. Such measurements had become fairly routine in the evaluation of septic patients in our MICU since the recent interest in the concept of relative AI.

Exclusion criteria included use of systemic glucocorticoids within 6 months prior to admission to the MICU, an established diagnosis of AI, use of etomidate or ketoconazole, or any condition requiring the use of glucocorticoids.

Study measures

All patients had cortisol levels measured within the first 48 h of the development of severe sepsis/septic shock, which in the majority of patients coincided with the first 48 h of MICU admission. The majority of cortisol levels were obtained between 04:00 h and 09:00 h. Patients with cortisol levels less than 552 nmol/l were included only if the value was obtained in the morning hours. Severity of illness was assessed by the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system at 24 h of admission to the MICU (Knaus et al., 1985).

Four groups were specified \( a \) \( \text{priori} \) based on serum cortisol levels: group 1 (cortisol \( \leq 345 \) nmol/l); group 2 (cortisol 345–552 nmol/l); group 3 (cortisol 552–1242 nmol/l); and group 4 (cortisol \( \geq 1242 \) nmol/l). A cortisol level \( \leq 345 \) nmol/l was chosen as the cut-off for the first cortisol group because data from the literature indicate very poor survival in critically ill patients who have a cortisol level \( \leq 345 \) nmol/l (Finlay & McKe, 1982; McKe & Finlay, 1983). We chose a cortisol level of 552 nmol/l for our second cut-off as it is considered an appropriate response to stress induced by hypoglycaemia based on the gold standard for diagnosis of AI by insulin tolerance test (Landon et al., 1966; Oelkers, 1996). Severe sepsis/septic shock most likely presents an even greater degree of stress than insulin-induced hypoglycaemia and at least a similar HPA response to stress would be expected (Marik & Zaloga, 2002). The third cut-off level for serum cortisol was set at 1242 nmol/l based on data from the literature that very high cortisol levels in critical illness are associated with worse outcomes (Sibbald et al., 1977; Jurney et al., 1987; Span et al., 1992; Jarek et al., 1993; Bouachour et al., 1995; Zaloga & Marik, 2001). Cortisol levels were measured by chemiluminescent assay in the routine hospital laboratory where the normal morning cortisol range is 138–552 nmol/l. The primary endpoints of the study were in-hospital and 90-day mortality.

Statistical methods

All tests were two-tailed, with an \( \alpha \) level of 0.05. Continuous variables were summarized using mean and SD. Categorical variables were summarized using percentages. The in-hospital and 90-day mortality in the four groups were compared using \( \chi^2 \) analysis. Kaplan–Meier 90-day analysis of survival were constructed for the four \( a \) \( \text{priori} \) groups and survival rates were compared by Mantel–Cox log-rank test. Differences in continuous variables between the four groups were compared using ANOVA. Correlations between APACHE II scores and serum cortisol levels, APACHE II scores and glucose levels, and glucose and cortisol levels were determined using Spearman correlation coefficients for all patients and then individually in each group. Statistical analyses were performed using StatView software (SAS Institute Inc. Version 5.0.1, Cary, NC, USA).

Results

Patient demographics

Data are given as mean \( \pm \) SD. The average patient age was 63 \( \pm \) 17 years, 70% of all patients were white and 54% were men. The average APACHE II score for all patients was 23 \( \pm \) 7,
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Consistent with severe critical illness. The average cortisol level for all patients was 883 ± 690 nmol/l. The average cortisol level for hospital survivors (n = 49) was 745 ± 855 nmol/l and for nonsurvivors (n = 51) was 1021 ± 386 nmol/l (P = 0.2 by Mann–Whitney test). Overall, 71% of patients were on mechanical ventilation at the time of enrolment in the study and 87% were hypotensive requiring the use of vasopressor agents to maintain haemodynamic stability. All patients had either severe respiratory failure and/or hypotension at the time of enrolment. Blood cultures were positive in 55% of patients. The most common sites of infection were the lungs at 53% followed by infections of the urinary tract and abdomen at 12% each.

Relationship between cortisol categories and outcomes

Table 1 summarizes the baseline characteristics and outcomes for all patients based on the four cortisol groups. In-hospital and 90-day mortality for all patients were 51% and 60%, respectively. The majority, 54 patients, had serum cortisol levels between 552 and 1242 nmol/l. Thirty patients had serum cortisol levels less than 552 nmol/l and 11 of these had cortisol levels ≤ 345 nmol/l. Sixteen patients had serum cortisol levels greater than 1242 nmol/l. There were more diabetes and HIV in patients in group 1 (cortisol ≤ 345 nmol/l), and more cancer in group 4 (cortisol ≥ 1242 nmol/l). Patients in the four cortisol groups were similar in terms of the need for mechanical ventilation, vasopressor use and prevalence of positive blood cultures.

<table>
<thead>
<tr>
<th>Cortisol group</th>
<th>Group 1 (≤ 345 nmol/l)</th>
<th>Group 2 (345–552 nmol/l)</th>
<th>Group 3 (552–1242 nmol/l)</th>
<th>Group 4 (≥ 1242 nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>19</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 15</td>
<td>56 ± 16</td>
<td>66 ± 17</td>
<td>65 ± 16</td>
</tr>
<tr>
<td>Male sex</td>
<td>54%</td>
<td>68%</td>
<td>49%</td>
<td>50%</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>24 ± 7</td>
<td>22 ± 7</td>
<td>22 ± 6</td>
<td>26 ± 7</td>
</tr>
<tr>
<td>% Mechanical ventilation</td>
<td>72%</td>
<td>84%</td>
<td>68%</td>
<td>81%</td>
</tr>
<tr>
<td>% Vasopressor use</td>
<td>81%</td>
<td>84%</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Duration of ICU stay</td>
<td>12 ± 16.6</td>
<td>9 ± 8.6</td>
<td>10 ± 11</td>
<td>6 ± 5</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>27 ± 18.6</td>
<td>24 ± 21</td>
<td>19 ± 14</td>
<td>12 ± 9</td>
</tr>
<tr>
<td>Preexisting conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>45%</td>
<td>10%</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>HIV</td>
<td>18%</td>
<td>5%</td>
<td>5-6%</td>
<td>0%</td>
</tr>
<tr>
<td>Cancer</td>
<td>10%</td>
<td>10%</td>
<td>17%</td>
<td>25%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>10%</td>
<td>26%</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>ESRD</td>
<td>18%</td>
<td>5%</td>
<td>13%</td>
<td>19%</td>
</tr>
<tr>
<td>% Positive blood cultures</td>
<td>63%</td>
<td>57%</td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>7.27 ± 3.3</td>
<td>7.98 ± 3.5</td>
<td>7.38 ± 3.0</td>
<td>9.88 ± 5.6</td>
</tr>
<tr>
<td>% In-hospital mortality</td>
<td>54%</td>
<td>53%</td>
<td>41%</td>
<td>81%*</td>
</tr>
<tr>
<td>% 90-day mortality</td>
<td>64%</td>
<td>55%</td>
<td>52%</td>
<td>87%‡</td>
</tr>
<tr>
<td>Preexisting conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESRD, end-stage renal disease; HIV, human immunodeficiency syndrome.
*P < 0.01 by χ² analysis; †P < 0.02 by Mantel–Cox log-rank test.

On χ² analysis, there was a statistically significant difference in in-hospital and 90-day mortality between the four groups (P < 0.01) as demonstrated in Table 1. However, most of this difference was due to the high mortality in group 4 (cortisol ≥ 1242 nmol/l) and after exclusion of this group from χ² analysis, there was no significant difference in mortality among the other three groups. Figure 1 demonstrates 90-day Kaplan–Meier survival analysis for the four cortisol groups. The survival analysis for patients with cortisol ≥ 1242 nmol/l was different from the other groups (P = 0.02, Mantel–Cox log-rank test). Exclusion of patients with cortisol ≥ 1242 nmol/l from the analysis revealed no difference in 90-day survival amongst the remaining three groups. Six of the patients in group 1 (cortisol ≤ 345 nmol/l) received hydrocortisone treatment (150–300 mg/day) but their mortality (50%) was not significantly different from five patients in the same group who did not receive hydrocortisone (60%). All 11 patients in this group were similar in terms of severity of illness. None of the patients in the other groups received hydrocortisone or any other form of glucocorticoid treatment.

Relationship between cortisol levels and APACHE II scores

There was no significant difference in APACHE II scores between the four cortisol groups (P = 0.24) as demonstrated in Fig. 2.

Correlation coefficients were determined between APACHE II scores and cortisol levels for all patients and for each cortisol group separately. These relationships are demonstrated in Fig. 3.
When all patients were analysed as one group, a positive correlation between APACHE II scores and cortisol levels was observed ($r = 0.21$, $P = 0.04$). Additionally, we correlated cortisol levels to APACHE II scores for each cortisol group separately; a positive correlation ($r = 0.44$, $P = 0.001$) was only observed in group 3 (cortisol 552–1242 nmol/l).

**Discussion**

The optimal range for serum cortisol levels in severe sepsis remains unclear. This factor, in addition to lack of uniform criteria for diagnosis of AI in severe sepsis has led to the reported incidence of AI varying from 1.5% to 54% (Sibbald et al., 1977; Finlay & McKee, 1982; Rothwell et al., 1991; Soni et al., 1995; Amman et al., 2000; Rivers et al., 2001; Marik and Zaloga, 2003). Our patients were chosen from a uniform population of critically ill patients with severe sepsis/septic shock who had APACHE II scores and mortality rates comparable to reported rates in the literature (Knaus et al., 1985; Angus et al., 2001). There was a wide range of cortisol levels in our patient population, although the majority of cortisol levels were between 552 and 1242 nmol/l.

In-hospital and 90-day mortality were significantly increased in patients with cortisol levels above 1242 nmol/l. Despite a higher mortality in this group, the severity of illness based on APACHE II scores was not significantly higher compared to the other three cortisol groups. Because APACHE II scores and cortisol levels are indicators of severity of illness, we expected a positive correlation between these two variables. Lack of a positive correlation between APACHE II scores and cortisol levels in this group suggests an inappropriately high cortisol response to stress (Fig. 3). It may be that an exaggerated HPA response to stress leading to very elevated cortisol levels worsens outcomes in this group of patients. In addition, the patients with cortisol levels above 1242 nmol/l were older and had a higher prevalence of cancer when compared to the other three groups. The contribution of these confounders to the higher mortality rate remains unknown. Patients in this group also had the shortest duration of hospital stay which was secondary to their high in-hospital mortality rate, as clearly indicated by the Kaplan–Meier survival analysis (Fig. 1). Overall, 30% of patients had cortisol levels less than 552 nmol/l, which may be low for the severity of illness and suggestive

![Fig. 1](image1.png)  
**Fig. 1** Ninety-day Kaplan–Meier survival curve for the four cortisol groups. Mortality is significantly increased for group 4 ($P = 0.02$ by Mantel–Cox log-rank test). □, Group 1; ○, group 2; ▽, group 3; △, group 4.

![Fig. 2](image2.png)  
**Fig. 2** Distribution of APACHE II scores amongst the four cortisol groups. The APACHE II score is similar amongst the four cortisol groups ($P = 0.24$ by ANOVA).
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Additionally, the prevalence of HIV was higher in patients with cortisol levels \( \leq 345 \text{ nmol/l} \), and in these individuals there may have been HIV involvement of the adrenal glands. The finding that mortality was not increased in patients with cortisol levels less than 552 nmol/l was surprising to us but our study may not have been powered to detect an increase in mortality in patients with lower cortisol levels. Again, a lack of correlation between cortisol levels and APACHE II scores may indicate that the low cortisol response to stress in groups 1 and 2 (cortisol \( \leq 552 \text{ nmol/l} \)) is inappropriate and represents dysfunctional HPA responses to stress. Indeed, a positive correlation between APACHE II scores and cortisol levels was only present in patients with cortisol levels between 552 and 1242 nmol/l (Fig. 3). Patients in group 1 (cortisol levels \( \leq 345 \text{ nmol/l} \)) also had the longest hospital and ICU duration of stay, which may suggest a delay in recovery time secondary to suboptimal adrenal responses.

Fig. 3 Relation between cortisol levels and APACHE II scores. These four graphs show the correlation between APACHE II scores and cortisol levels in each cortisol group. A statistically significant positive relationship is only demonstrated for group 3 (cortisol 552–1242 nmol/l). The lack of a positive correlation in the other three groups may indicate a dysregulation of the HPA axis.

Fig. 4 Distribution of glucose levels upon enrolment amongst the four cortisol groups. Even though mean glucose was higher in patients with cortisol > 1242 nmol/l, there was no statistically significant difference between the four groups by ANOVA.

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We did not observe a survival benefit among patients in the lowest cortisol group (cortisol ≤ 345 nmol/l) who received hydrocortisone but this most likely is related to the small number of subjects in this group. There is emerging data that physiologic hydrocortisone replacement in patients with septic shock and relative AI (defined by either a suboptimal rise in cortisol levels after stimulation with ACTH or a random cortisol level < 690 nmol/l) improves survival and decreases duration of vasopressor use (Annane et al., 2002; Marik & Zaloga, 2003). However, our study was not designed to evaluate the usefulness of hydrocortisone therapy in patients with septic shock.

We did not measure ACTH levels or cortisol responses to ACTH stimulation. The adrenal response to severe endogenous stress has always been a superior test for diagnosis of AI compared to the response to exogenous ACTH stimulation (Marik & Zaloga, 2003). Hence, insulin-induced hypoglycaemia has been regarded as the gold standard diagnostic method for AI (Landon et al., 1966; Oelkers, 1996). Severe sepsis/septic shock leads to an even greater stimulation of the HPA axis than that produced by hypoglycaemia, as reflected by the elevated basal serum cortisol levels in this state (Zaloga and Marik, 2001). Furthermore, sepsis may be associated with transient dysfunction of the hypothalamic-pituitary axis due to release of cytokines that interfere with ACTH release (Keri et al., 1981; Catalano et al., 1984; Gaillard et al., 1990; Jaattela et al., 1991; Zaloga & Marik, 2001). This latter abnormality can lead to secondary adrenal insufficiency and, as it is of recent onset, a normal cortisol response to ACTH is expected. As a result the diagnosis of AI may be missed if the criteria are solely based on a rise in serum cortisol levels after ACTH stimulation.

There are limitations in our study. First, not all serum cortisol levels were obtained at the same time, although the majority were taken in the morning hours within the first 24 h of the development of septic shock. As the diurnal variability of serum cortisol and circadian rhythm of melatonin are lost in the first few days of critical illness and sepsis, this should not be a significant factor (Bornstein et al., 1998; Voerman et al., 1992; Mundigler et al., 2002). Additionally, patients with cortisol levels less than 552 nmol/l were only included in the study if cortisol levels were obtained in the morning hours. A second limitation includes a possibility of selection bias as we included only septic patients who had a cortisol level obtained within the first 48 h of septic shock. There may have been a higher suspicion for AI among these patients leading to inclusion of a higher percentage of patients with low cortisol levels in the study. However, this would not influence the main objective of our study which was the relationship between cortisol levels and mortality.

On the other hand, the strengths of our study include the fact that it is one of the largest prospective observational studies examining the relationship between cortisol levels and survival in a group of patients with a uniform definition of severe sepsis/septic shock. Hence, the variation in cortisol responses is a true indicator of the variation in the adrenal response to septic shock. Additionally, it is the only study evaluating the relationship among cortisol levels, APACHE II scores and glucose levels.

Our findings confirm those of earlier studies that cortisol levels are good predictors of outcome in septic shock (Span et al., 1992; Jarek et al., 1993). Prior studies have demonstrated that very high or low cortisol levels in sepsis are associated with worse outcomes (Sibbald et al., 1977; Finlay & McKee, 1982; Jurney et al., 1987; Soni et al., 1995). Our study demonstrated a statistically significant higher mortality only in patients with very high serum cortisol levels (group 4, cortisol ≥ 1242 nmol/l). Establishment of standard methods and criteria for diagnosis of AI in sepsis and critical illness is necessary as indiscriminate use of exogenous glucocorticoids may worsen outcome in certain subsets of septic patients.

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