Hypothalamic–pituitary–adrenal axis response to the severity of illness in non-critically ill patients: does relative corticosteroid insufficiency exist?

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Abstract
Objective: Relative corticosteroid insufficiency may be common in critically ill patients and is associated with a poor outcome; however, the response of the hypothalamic–pituitary–adrenal (HPA) axis in nursed patients is not known. Our aim was to evaluate the response of HPA axis to the severity of illness in non-critically ill nursed (NCIN) patients and the clinical outcome.

Subjects and methods: Fifty-six nursed patients who were divided into four groups (stroke, mild disease, sepsis and severe sepsis) as well as a control group (n = 15) were studied. At admission (day 1), cortisol and ACTH were measured and a low-dose (1 mg) corticotrophin test was performed, followed 2 h later by a standard-dose (250 μg) corticotrophin test. Diurnal variation of cortisol was obtained on day 2. A second identical set of low-dose and standard-dose corticotrophin tests were performed on day 5 or 6 (recovery phase).

Results: In patients with stroke and severe sepsis, cortisol had the highest values and its diurnal variation was abolished. Dissociation of ACTH and cortisol was found in all patients. The Δmax of cortisol after the 1-mg corticotrophin test did not differ among the groups, while after the 250-μg corticotrophin test, it was borderline higher in controls. The ratio of responders (Δmax of cortisol ≥ 9 μg/dl) to non-responders after 1- or 250-μg corticotrophin test did not differ among patients and controls. All patients had a good outcome without glucocorticoid treatment.

Conclusions: Depending on the severity of illness, mild alterations in the HPA axis occurred. However, relative corticosteroid insufficiency was not confirmed in NCIN patients.

Introduction
Illness of various degrees of severity and hospital care result in a stress response, which is mainly mediated by the hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal system (1, 2). Although an increasing number of studies have been performed on the function of the axis during illness (3, 4), the effectiveness of the axis in severity of illness with respect to cortisol secretion remains unclear. In addition, the use of cortisol treatment in accordance with the severity of illness, especially in acute phase, is controversial. It remains to be established if the administration of glucocorticoids that improves the outcome of critically ill patients (5, 6) also improves the outcome of non-critically ill nursed (NCIN) patients.

A consensus statement was published recently with regard to the diagnosis and management of corticosteroid deficiency in patients with critical illness (critical illness-related corticosteroid insufficiency, CIRCI) by an international task force of the American College of Critical Care Medicine (7). According to the task force, the recommendations for treatment with corticosteroids are limited to septic shock and acute respiratory distress syndrome (ARDS).

CIRCI is caused by adrenal insufficiency and tissue resistance to corticosteroids, and it is characterized by an exaggerated and protracted proinflammatory response (1). The diagnosis of tissue resistance to corticosteroid is difficult (8). According to Annane et al (9), the best criteria for the diagnosis of adrenal insufficiency in critically ill patients are an increase in total serum cortisol of < 9 μg/dl after the administration of corticotrophin (250 μg) or a random total cortisol measurement of < 10 μg/dl. However, a current concept by Bornstein (10) suggested that the best available test for the diagnosis of adrenal insufficiency in critical illness is the 1-μg corticotrophin stimulation test. However, although this test is more sensitive, it is not accepted by all (7, 9).

Review of the extensive literature in this area highlights several important unresolved issues with respect to the function of the HPA axis both in physiological states and under the stress of illness. It is...
not established if the above-mentioned diagnostic criteria for CIRCI could be used in NCIN patients and if the dysfunction of the HPA axis could determine the clinical outcome.

It is well documented that glucocorticoid synthesis and release by the adrenal glands are regulated by the HPA axis. However, the picture has subsequently become more complex, and it seems that although ACTH is essential for this release, alternative pathways exist for the regulation of adrenocortical function. Dissociation between the levels of ACTH and glucocorticoids during foetal, postnatal and adult life has been demonstrated (11, 12). In addition, clinical studies report the dissociation of ACTH and glucocorticoid levels in critical illness, inflammation and mental disorders. Cytokines, vasoactive factors and neuropeptides seem to play an important role in the modulation of the adrenal response to severe stress, and act independently of ACTH (12).

There is a need for more research to evaluate the adrenal response to the severity of illness in the acute and recovery phases in NCIN patients to detect if relative corticosteroid insufficiency exists, as well as the need for glucocorticoid treatment.

Subjects and methods

This is a prospective study performed between September 2007 and October 2008 in the Department of Internal Medicine of the University Hospital of Patras. Fifty-six patients who had been admitted to the hospital were divided into four groups according to the severity of their illness: group 1 comprised ten patients (seven males/three females) with ischaemic stroke as mild disease) and they had a mean age of 62.4 ± 13.8 years and a mean BMI of 27.5 ± 3.9 kg/m²; group 3 comprised 20 patients (8 males/12 females) with sepsis and they had a mean age of 58.5 ± 8.9 years and a mean BMI of 25.6 ± 5.6 kg/m² and group 4 comprised 11 patients (5 males/6 females) with severe sepsis and they had a mean age of 61.3 ± 9.3 years and a mean BMI of 26.2 ± 4 kg/m². Fifteen healthy controls (seven males/eight females) were also evaluated (mean age 59.6 ± 5.1 years; mean BMI 26.1 ± 2.2 kg/m²). The controls (group 5) were recruited from the endocrinology outpatient clinic, and were mainly staff members, relatives or friends who were exposed to the stressful conditions of the hospital.

Sepsis was defined as the clinical syndrome of systemic inflammatory response (SIRS) with suspected or proven microbial aetiology. SIRS was diagnosed based on two or more of the following conditions: fever (temperature > 38 °C) or hypothermia (temperature < 36 °C), tachycardia (> 90 beats/min), tachypnoea (> 24 breaths/min), leucocytosis or leucopaenia (white blood cells > 12 000 or < 4000 cells/μl respectively) or immature neutrophils (bands > 10%) (13). Severe sepsis was defined as sepsis with one or more signs of organ dysfunction as follows: i) Cardiovascular: arterial systolic blood pressure ≤ 90 mmHg or mean arterial pressure ≤ 70 mmHg that responded to administration of intravenous fluid. ii) Renal: urine output < 0.5 ml/kg per h for 1 h despite adequate fluid resuscitation. iii) Respiratory: PaO₂/FiO₂ ≤ 250 or; if the lung was the only dysfunctional organ, ≤ 200. iv) Haematological: platelet count < 80 000/μl or 50% decrease in platelet count from the highest value recorded over the previous 3 days. v) Unexplained metabolic acidosis: a pH ≤ 7.30 or a base deficit ≥ 5.0 mEq/l and a plasma lactate level > 1.5 times the upper limit of normal for the reporting laboratory. vi) Adequate fluid resuscitation: pulmonary artery wedge pressure ≥ 12 mmHg or central venous pressure ≥ 8 mmHg (13). Severe sepsis was evaluated using the sepsis-related organ failure assessment (SOFA) score (14).

No patients had a history of adrenal insufficiency and they had not received any drug known to affect the HPA axis such as rifampicine (15, 16), ketoconazole (17), or other antifungal agents or anticonvulsants (18). The patients did not receive corticosteroids, including inhaled preparations, or catecholamines during the study.

Informed written consent was obtained, and the study protocol was approved by the ethics committee of the hospital.

Study design

On admission (day 1), a blood count and biochemical tests were performed, and baseline serum samples for cortisol, triiodothyronine (T₃), thyroxine (T₄), and TSH, and a plasma sample for ACTH were obtained from each patient (baseline values). Also on admission, each patient had undergone a low-dose (1 μg) corticotrophin test and 2 h later a standard-dose (250 μg) corticotrophin test (tetracosactrin 0.25 mg, Synacthen; Ciba-Geigy, Rueil-Malmaison, France). The tests were performed as follows: after a baseline serum cortisol concentration was drawn, the low-dose corticotrophin test was performed by administering 1 μg corticotrophin intravenously. Samples for the measurements of serum cortisol were obtained at 30 (t30) and 60 (t60) minutes after injection. Two hours after the low-dose corticotrophin test, the standard-dose (250 μg) corticotrophin test was performed by administering 250 μg corticotrophin intravenously. Samples for the measurements of serum cortisol were taken at t30 and t60 (19). The cortisol response (Δₜ₉₀) was defined as the highest cortisol concentration at t30 or t60 minus the baseline.
serum cortisol. Responders were classified as patients with $\Delta_{\text{max}} > 9 \mu g/dl$, and non-responders were classified as the subjects with $\Delta_{\text{max}} \leq 9 \mu g/dl$.

On day 2, samples were collected from each patient for the measurements of serum cortisol at 0800, 1400, 2000 and 0200 h.

Healthy controls who attended the hospital for 1 day underwent identical low-dose (1 µg) and standard-dose (250 µg) corticotrophin tests.

Three out of the 11 patients with severe sepsis (group 4) died on day 3 or 4. These patients were transferred to the intensive care because of the deterioration of their condition after admission, and no further tests were performed after day 1.

On day 5 or 6 of nursing, during recovery, 7 of 20 patients with sepsis (group 3) and the 8 survivors with severe sepsis (group 4) were tested again with the low-dose (1 µg) and standard-dose (250 µg) corticotrophin tests.

### Assays

Serum samples were centrifuged immediately, aliquoted and stored at $-70^\circ$C until assayed. Plasma samples for the measurement of ACTH were collected under chilled conditions and centrifuged in a cooled centrifuge. Serum cortisol, thyroid hormones and plasma ACTH were measured by chemiluminescence immunoassay (Modular Analytics E170, Roche, and Hitachi). The samples were assayed in a single large batch. For cortisol, the within- and between-run coefficient of variation (CV) values were 1.5–1.7 and 1.8–2.8%, and the lower detection limit was 0.018 µg/dl. For ACTH, the within- and between-run CV values were 0.6–2.7 and 3.5–5.4%, and the lower detection limit was 1.0 µg/ml. For $T_3$, $T_4$ and TSH respectively the within- and between-run CV values were 0.6–2.7 and 3.3–7.2%, and the lower detection limits were 0.195 ng/ml, 0.42 µg/dl and 0.005 µU/ml.

### Statistical analysis

All values are expressed as the mean±s.d., and statistical significance was set at $P<0.05$. Mean values were compared between groups by one-way ANOVA and post hoc analysis using the Bonferroni multiple comparison test, or independent-samples $t$-tests. Mean values within groups were compared by ANOVA for repeated measurements or paired $t$-tests. For categorical variables, comparisons between groups were performed using the $\chi^2$ or Fisher’s exact test. Pearson’s correlation tests were used to assess the relationships among several parameters. Data were analyzed with the use of SPSS version 16 (SPSS, Inc., Chicago, IL, USA).

### Results

#### Baseline measurements and low- and standard-dose corticotrophin tests on day 1

No differences were detected among the groups with respect to age, BMI or gender. Baseline measurements from all groups are presented in Table 1. Mean serum ACTH levels did not differ among the groups, but the mean serum cortisol levels were significantly different (one-way ANOVA, $P<0.001$). Post hoc analysis revealed that the mean cortisol levels in group 4 were higher than those in groups 2, 3 and 5 ($P<0.001$), but they did not differ from that in group 1. Mean albumin levels differed among groups (one-way ANOVA, $P<0.001$), and the lowest value was obtained in group 4 (post hoc analysis, $P<0.001$). Mean serum $T_4$ and TSH did not differ among the groups, whereas the $T_3$ levels were

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Ischaemic stroke (group 1; $n=10$)</th>
<th>Mild disease (group 2; $n=15$)</th>
<th>Sepsis (group 3; $n=20$)</th>
<th>Severe sepsis (group 4; $n=11$)</th>
<th>Controls (group 5; $n=15$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (µg/dl)</td>
<td>24.4±9.37</td>
<td>19.7±6.5</td>
<td>21.8±7.1</td>
<td>38.0±24.9</td>
<td>13.1±5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>13.6±9.7</td>
<td>14.7±10.5</td>
<td>18.3±7.2</td>
<td>11.2±12.7</td>
<td>19.3±10.6</td>
<td>NS</td>
</tr>
<tr>
<td>$T_3$ (µg/dl)</td>
<td>0.9±0.3</td>
<td>0.9±0.2</td>
<td>0.8±0.19</td>
<td>0.5±0.12</td>
<td>1.0±0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$T_4$ (µg/dl)</td>
<td>8.2±1.3</td>
<td>8.9±1.4</td>
<td>7.4±1.7</td>
<td>7.8±2.0</td>
<td>8.2±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>TSH (µU/ml)</td>
<td>1.6±1.1</td>
<td>1.3±1.2</td>
<td>0.98±0.6</td>
<td>1.5±1.4</td>
<td>1.9±1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.7±0.5</td>
<td>3.6±0.4</td>
<td>3.5±0.5</td>
<td>3.6±0.4</td>
<td>3.6±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$\Delta_{\text{max}}-1\mu g\text{ACTH (µg/dl)}$</td>
<td>12.3±6.9</td>
<td>10.3±4.9</td>
<td>10.4±4.1</td>
<td>10.0±5.6</td>
<td>13.6±4.6</td>
<td>NS</td>
</tr>
<tr>
<td>$\Delta_{\text{max}}-250\mu g\text{ACTH (µg/dl)}$</td>
<td>21.7±9.2</td>
<td>18.7±7.1</td>
<td>17.0±6.6</td>
<td>16.3±7.8</td>
<td>23.9±8.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Responders/non-responders after 1 µg ACTH</td>
<td>7/3</td>
<td>9/6</td>
<td>12/8</td>
<td>7/4</td>
<td>13/2</td>
<td>NS</td>
</tr>
<tr>
<td>Responders/non-responders after 250 µg ACTH</td>
<td>9/1</td>
<td>15/0</td>
<td>18/2</td>
<td>9/2</td>
<td>15/0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group 1, ischaemic stroke; group 2, mild disease; group 3, sepsis; group 4, severe sepsis; group 5, controls. $\Delta_{\text{max}}$ of cortisol maximum–cortisol baseline; $\Delta_{\text{max}}-1\mu g\text{ACTH} = \Delta_{\text{max}}$ after 1 µg ACTH; $\Delta_{\text{max}}-250\mu g\text{ACTH} = \Delta_{\text{max}}$ after 250 µg ACTH; Responders, $\Delta_{\text{max}} > 9$ µg/dl.
significantly different (one-way ANOVA, $P<0.001$). Post hoc analysis showed that the mean T$_3$ levels in group 4 were lower than those in the other groups ($P<0.05$ and $P<0.001$ respectively).

Mean serum cortisol levels at the baseline did not correlate with the mean ACTH levels in all groups of patients, but they did correlate with the SOFA score in group 4 (Pearson $r=0.77$, $P<0.001$), and they were inversely correlated with the mean T$_3$ levels in all patient groups (Pearson $r=-0.39$, $P<0.001$).

The $\Delta_{\text{max}}$ of cortisol after the 1-$\mu$g corticotrophin test did not differ among the groups. However, the differences in $\Delta_{\text{max}}$ of cortisol after the 250-$\mu$g corticotrophin test were borderline significant ($P=0.05$). The $\Delta_{\text{max}}$ of cortisol after the 250-$\mu$g corticotrophin test tended to be higher in the control group than in patients with sepsis or severe sepsis (independent-samples t-test, $P<0.05$).

The $\Delta_{\text{max}}$ of cortisol was higher after the 250-$\mu$g corticotrophin test than after the 1-$\mu$g corticotrophin test in all groups of patients (paired t-tests, $P<0.001$) and in healthy controls (paired t-tests, $P<0.01$). The $\Delta_{\text{max}}$ of cortisol was inversely correlated with baseline cortisol after the 1 and 250-$\mu$g corticotrophin tests. (Pearson $r=-0.475$, $P<0.001$; Pearson $r=-0.335$, $P<0.001$ respectively).

Baseline characteristics of the responders and non-responders in all groups for both low- and standard-dose corticotrophin tests are presented in Table 1.

The baseline characteristics of the three patients with severe sepsis who died on the 3rd and 4th days of hospitalization are presented in Table 2.

During nursing, none of the patients developed hypotension or any electrolyte disorders.

**Circadian rhythm**

The diurnal variation in serum cortisol disappeared in groups 1 and 4, but it was maintained in groups 2 and 3 (Table 3). In the four groups of patients, the mean serum cortisol at midnight was > 2.5 $\mu$g/dl, which is the normal level of cortisol in subjects who are awake (20).

**Table 2** Baseline characteristics and cortisol response to low and standard doses of ACTH at admission (day 1) in three non-survivors with severe sepsis (group 4).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cortisol (pg/ml)</th>
<th>ACTH (pg/ml)</th>
<th>T$_3$ (pg/ml)</th>
<th>T$_4$ (pg/ml)</th>
<th>TSH (ng/ml)</th>
<th>ALB (g/dl)</th>
<th>$\Delta_{\text{max}}$–1 $\mu$g ACTH (pg/ml)</th>
<th>$\Delta_{\text{max}}$–250 $\mu$g ACTH (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41.5</td>
<td>14.8</td>
<td>0.41</td>
<td>8.1</td>
<td>0.76</td>
<td>2.8</td>
<td>9.34</td>
<td>17.7</td>
</tr>
<tr>
<td>2</td>
<td>63.4</td>
<td>1.02</td>
<td>0.42</td>
<td>7.7</td>
<td>0.82</td>
<td>1.8</td>
<td>7.3</td>
<td>6.9</td>
</tr>
<tr>
<td>3</td>
<td>100.5</td>
<td>1.00</td>
<td>0.60</td>
<td>4.1</td>
<td>0.005</td>
<td>2</td>
<td>2.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

**Table 3** Circadian rhythm of serum cortisol on the first day after admission (day 2) in four groups of patients. ANOVA for repeated measurements was performed in each group. Values are expressed as the mean±s.d.

<table>
<thead>
<tr>
<th>Ischaemic stroke</th>
<th>Mild disease</th>
<th>Sepsis</th>
<th>Severe sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(group 1; $n=10$)</td>
<td>(group 2; $n=15$)</td>
<td>(group 3; $n=20$)</td>
<td>(group 4; $n=11$)</td>
</tr>
<tr>
<td>Cortisol 0800 (µg/dl)</td>
<td>27.6±14.6</td>
<td>19.7±6.9</td>
<td>27.3±6</td>
</tr>
<tr>
<td>Cortisol 1400 (µg/dl)</td>
<td>26.7±10.1</td>
<td>16±6.4</td>
<td>23.9±7.6</td>
</tr>
<tr>
<td>Cortisol 2000 (µg/dl)</td>
<td>22.5±8.4</td>
<td>13.8±6.5</td>
<td>17.6±6.4</td>
</tr>
<tr>
<td>Cortisol 0200 (µg/dl)</td>
<td>20.6±10.2</td>
<td>10.3±5.2</td>
<td>13.7±5.3</td>
</tr>
</tbody>
</table>

**Cortisol response to both the low- and standard-dose corticotrophin tests in patients with sepsis and severe sepsis during acute and recovery phases of illness**

On day 5 or 6 during recovery, 7 of 20 patients with sepsis (group 3) and 8 survivors with severe sepsis (group 4) underwent additional testing with the low-dose (1 $\mu$g) and standard-dose (250 $\mu$g) corticotrophin tests.

In the patients in group 3, the mean cortisol levels were slightly higher in the acute phase than in the recovery phase ($P=0.07$), whereas the mean plasma ACTH levels did not differ. The $\Delta_{\text{max}}$ of cortisol level after the 1-$\mu$g corticotrophin test did not differ between the acute phase of illness (day 1) and the recovery phase (day 5 or 6). However, $\Delta_{\text{max}}$ of cortisol after the 250-$\mu$g corticotrophin test was significantly higher in the recovery phase (Table 4).

The patients from group 4 who survived had mean cortisol levels that were higher in the acute phase than in the recovery phase, whereas their mean plasma ACTH and $\Delta_{\text{max}}$ of cortisol after both corticotrophin tests did not differ between the acute and recovery phases (Table 5).
Table 5: Mean cortisol, ACTH, Δmax - 1 μg ACTH and Δmax - 250 μg ACTH at baseline (acute phase) and on the 5th or 6th day of hospitalization (recovery phase) in eight survivors with severe sepsis.

<table>
<thead>
<tr>
<th></th>
<th>Acute phase</th>
<th>Recovery phase</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (µg/dl)</td>
<td>26.59 ± 9.4</td>
<td>18.8 ± 8.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>11.45 ± 4.98</td>
<td>20.3 ± 13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Δmax - 1 μg ACTH (µg/dl)</td>
<td>11.5 ± 5</td>
<td>11.3 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Δmax - 250 μg ACTH (µg/dl)</td>
<td>19.2 ± 5.85</td>
<td>20.04 ± 8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Responders/non-</td>
<td>6/2</td>
<td>5/3</td>
<td>NS</td>
</tr>
<tr>
<td>responders after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 μg ACTH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders/non-</td>
<td>8/0</td>
<td>8/0</td>
<td>NS</td>
</tr>
<tr>
<td>responders after</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>250 μg ACTH</td>
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</table>
In the current study, all the patients with severe sepsis who recovered had $\Delta_{\text{max}}$ of cortisol $\geq 9 \mu g/dl$ after the standard-dose corticotrophin stimulation test in the acute phase of disease (responders). Two patients with sepsis recovered despite the fact that they had $\Delta_{\text{max}}$ of cortisol $< 9 \mu g/dl$ after the standard-dose corticotrophin test in the acute phase of disease (non-responders) without corticosteroid treatment. This fact confirms our opinion that in NCIN patients, the degree of activation of their HPA axis and cortisol production correlates with the severity of their disease and is sufficient for their general adaptation.

We evaluated patients with sepsis and severe sepsis during the acute and recovery phases of illness. In the recovery phase, patients with sepsis had a baseline level of cortisol borderline lower and a significantly higher $\Delta_{\text{max}}$ of cortisol after the standard-dose (250 mg) corticotrophin test than in the acute phase, which indicated that the HPA axis was recovering. Patients with severe sepsis had a significantly lower baseline cortisol but a similar $\Delta_{\text{max}}$ of cortisol after the standard-dose (250 mg) corticotrophin test in the recovery phase as compared to the acute phase. This was probably due to the short interval between the acute and recovery phases and the inability of the HPA axis to recover or probably due to non-reproducibility of these tests during illness (25). The mechanisms that lead to alterations in the HPA axis during illness are complex and still poorly understood.

In conclusion, we believe that mild alterations in the HPA axis occur in NCIN patients, but relative corticosteroid insufficiency could not be established. None of the study patients received glucocorticoid therapy, and all but three patients with severe sepsis, who were transferred to the intensive care unit and died, had a good outcome. Recommendations for the management of septic shock and ARDS with glucocorticoids have been published (7), and we agree with those. A limitation of our study is the relatively small sample size. We need further prospective controlled numerous studies to confirm the effective level of baseline and stimulated cortisol and if corticosteroid treatment is necessary in the acute phase of the disease in NCIN patients. During nursing patients with non-critical illness, physicians must be aware of clinical signs and symptoms that are suspicious for glucocorticoid insufficiency.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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