Changes in serum cortisol levels during community-acquired pneumonia: The influence of dexamethasone

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Summary
In community-acquired pneumonia (CAP), the cortisol level on admission can be a useful biomarker for prognosis. Serial cortisol measurements during the clinical course of disease and their association with disease outcome have never been reported. Furthermore, the time to recovery of the hypothalamic-pituitary-adrenal axis after a short course of dexamethasone during infection is unclear.

We analyzed data from 270 hospitalized patients with CAP. Total serum cortisol was measured on presentation, day 1, 2, 4, and on control visit (day 30). Intensive care unit (ICU) admission and mortality were assessed. Additionally, to study the influence of dexamethasone on the kinetics of the cortisol response, we analyzed serial cortisol values of 43 patients treated with a four-day regimen of dexamethasone 5 mg.

During hospital stay, 26/270 patients (9.6%) were admitted to the ICU and 15/270 patients (5.6%) died. Compared to patients with an uneventful recovery, cortisol on presentation was
Main text

Cortisol, the predominant corticosteroid secreted by the adrenal cortex, is an important endogenous regulator of inflammation. During an infectious episode, cortisol production increases, and exerts anti-inflammatory and immunosuppressive activities. In patients with community-acquired pneumonia (CAP), a high serum cortisol at the moment of hospital admission is associated with an adverse outcome. Therefore, cortisol could be a useful biomarker for prognosis in CAP. To our knowledge, serial cortisol measurements over the course of disease and their association with disease outcome have never been reported. Synthetic corticosteroids are attractive as adjuvant therapy in CAP, although conflicting data have been published. A potential risk of corticosteroids is secondary adrenal insufficiency. The time to recovery of the hypothalamic-pituitary-adrenal (HPA) axis after a short course of dexamethasone during infection is unclear. For these reasons, we determined serum cortisol in patients with CAP on hospital admission and during the clinical course, until patients were recovered.

We analyzed data from two clinical studies carried out in two teaching hospitals in the Netherlands. Both studies enrolled patients with confirmed pneumonia, using identical inclusion criteria. The study methods have been described previously. Patients who were immunocompromised, on immunosuppressive therapy (including oral corticosteroids), or who required immediate admission to the intensive care unit (ICU) were excluded. For the present study, patients using oral contraceptives, ketoconazole, or patients receiving corticosteroids during hospital stay were also excluded. Additionally, we analyzed 43 randomly selected patients receiving dexamethasone as part of a clinical trial to explore the effect of dexamethasone on cortisol. Total serum cortisol was measured on presentation, on day 1, 2, and 4 (at 8 A.M.), and on control visit on day 30 by immunoassay (Calbiotech, Spring Valley, USA). Statistical analyses were performed using SPSS 18.0 (Chicago, USA). A two-tailed p-value <0.05 was considered significant. Patients were excluded from the study after ICU admission. We measured differences in cortisol, albumin and C-reactive protein (CRP) with the Students T-test or the Mann–Whitney U test as appropriate. Logistic regression was used to assess possible confounding between variables.

270 patients were analyzed (mean age 62.3 ± 18.0 years; 60% male). The mean pneumonia severity index (PSI) score was 86.5 ± 35.5 and 107/270 patients (40%) were classified as PSI class IV-V. Patients presented at the hospital at any given moment of the day. The cortisol level on presentation therefore could be biased by circadian effects. However, during critical illness the circadian rhythm is expected to be overridden. To determine whether the circadian rhythm of cortisol was lost on presentation, the time of cortisol measurement was plotted against the height of cortisol. Subsequently, the Kruskal–Wallis test was used to test for differences in height of cortisol. Indeed, we found no association between cortisol level and time of the day (p=0.51). Cortisol was higher in patients with inhaled corticosteroids at home (305 μg/L, IQR 176-527), compared to without (231 μg/L, IQR 153-374) (p=0.03).

During hospital stay, 26/270 patients (9.6%) were admitted to the ICU and 15/270 patients (5.6%) died. Cortisol on presentation was significantly higher in patients who died or were admitted to the ICU (n = 34, 360 μg/L, IQR 209-597), compared to patients with an uneventful recovery (238 μg/L, IQR 151-374) (p=0.01). This was independent of the use of inhaled corticosteroids at home. Serum albumin did not differ significantly between both groups (41.1 ± 9.3 g/L vs. 43.6 ± 7.6 g/L) (p=0.09). In patients with an adverse outcome cortisol remained significantly higher in patients with an adverse outcome (360 μg/L, IQR 209-597 vs. 238 μg/L, IQR 151-374) (p=0.01), and also remained significantly higher throughout the course of disease. Dexamethasone treatment resulted in nearly complete suppression of the endogenous cortisol production after the first dose, but cortisol production was fully recovered on control visit.

In conclusion, we showed that an adverse outcome of CAP was associated with persisting higher total serum cortisol throughout the course of disease. Delta-cortisol could be another meaningful biomarker in CAP. Next, our data indicate that a four-day dexamethasone regimen during CAP does not lead to prolonged secondary adrenal insufficiency.

Figure 1 Changes in serum cortisol in hospitalized patients with community-acquired pneumonia. Total serum cortisol levels are shown for patients with an uneventful recovery (panel A) and for patients who died or were admitted to the ICU (panel B). Data points for individual patients are shown; horizontal bars indicate median values. Asterisks indicate a significant difference (p < 0.05) between both groups on corresponding days.
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Table 1 Prediction of adverse clinical outcome (combined endpoint mortality/ICU admission) in community-acquired pneumonia: results from Receiver Operator Characteristics (ROC) curve analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients (total n = 270)</th>
<th>AUC 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol^a</td>
<td>266</td>
<td>0.63 0.53–0.74</td>
</tr>
<tr>
<td>Cortisol^a &amp; Δ-cortisol 0-1</td>
<td>226</td>
<td>0.68 0.54–0.83</td>
</tr>
<tr>
<td>Cortisol^a &amp; Δ-cortisol 0-2</td>
<td>218</td>
<td>0.81 0.71–0.91</td>
</tr>
<tr>
<td>Cortisol^a &amp; Δ-cortisol 0-4</td>
<td>186</td>
<td>0.88 0.81–0.94</td>
</tr>
<tr>
<td>CRP^a</td>
<td>270</td>
<td>0.65 0.55–0.75</td>
</tr>
<tr>
<td>CRP^a &amp; Δ-cortisol 0-1</td>
<td>226</td>
<td>0.66 0.53–0.79</td>
</tr>
<tr>
<td>CRP^a &amp; Δ-cortisol 0-2</td>
<td>218</td>
<td>0.73 0.56–0.90</td>
</tr>
<tr>
<td>CRP^a &amp; Δ-cortisol 0-4</td>
<td>186</td>
<td>0.75 0.52–0.98</td>
</tr>
<tr>
<td>CURB-65^a</td>
<td>205</td>
<td>0.66 0.55–0.76</td>
</tr>
<tr>
<td>CURB-65^a &amp; Δ-cortisol 0-1</td>
<td>173</td>
<td>0.71 0.60–0.83</td>
</tr>
<tr>
<td>CURB-65^a &amp; Δ-cortisol 0-2</td>
<td>161</td>
<td>0.76 0.59–0.92</td>
</tr>
<tr>
<td>CURB-65^a &amp; Δ-cortisol 0-4</td>
<td>142</td>
<td>0.70 0.51–0.88</td>
</tr>
<tr>
<td>PSI score^a</td>
<td>270</td>
<td>0.74 0.64–0.84</td>
</tr>
<tr>
<td>PSI score^a &amp; Δ-cortisol 0-1</td>
<td>226</td>
<td>0.77 0.67–0.88</td>
</tr>
<tr>
<td>PSI score^a &amp; Δ-cortisol 0-2</td>
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<td>0.80 0.67–0.93</td>
</tr>
<tr>
<td>PSI score^a &amp; Δ-cortisol 0-4</td>
<td>186</td>
<td>0.77 0.63–0.91</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; CURB-65, CURB-65 Severity Score for Community-Acquired Pneumonia; Δ, delta; PSI score, Pneumonia Severity Index score.

^a Measured on the day of presentation.

Significantly higher throughout the course of disease, compared to patients with an uneventful recovery (Fig. 1).

Based on the association between the course of cortisol during CAP and clinical outcome, we hypothesized that the change in serum cortisol from day 0 to day 1, 2 or 4 (delta (Δ) cortisol 0-1, 0-2, or 0-4) could be a better prognostic biomarker in CAP. To assess the predictive value of Δ-cortisol, Receiver Operator Characteristics (ROC) curve analysis was performed. Δ-cortisol 0-4 appeared to be the best predictor for adverse clinical outcome (AUC 0.73, 95% CI 0.53–0.93), followed closely by Δ-cortisol 0-2 (AUC 0.72, 95% CI 0.56–0.89). The additional predictive value of Δ-cortisol to the initial cortisol level or other biomarkers or clinical scores was calculated using binary regression and ROC curve analysis. When Δ-cortisol 0-4 or Δ-cortisol 0-2 was added to the cortisol level on presentation, the prognostic accuracy improved substantially (Table 1). Moreover, the predictive value of other commonly used biomarkers and clinical scores in CAP also improved considerably when Δ-cortisol 0-4 or Δ-cortisol 0-2 was added (Table 1).

In order to study the influence of dexamethasone on the kinetics of the cortisol response, 43 randomly selected patients treated with dexamethasone were analyzed in detail. These patients received a four-day course of dexamethasone 5 mg intravenously once a day during hospital stay, starting on the day of presentation. We analyzed the decrease of cortisol from day 0 to day 2 because all patients were at least 24 h on dexamethasone on day 2. As expected, dexamethasone treatment resulted in nearly complete suppression of endogenous cortisol production in all patients (mean decrease of 87%). Cortisol levels on day 30 (range 25–35) were within the normal physiological range, without apparent differences between the dexamethasone and the control group (69 µg/L, IQR 45–110 vs. 67 µg/L, IQR 44–106) (p=0.87). Both groups had low CRP concentrations on day 30 (5.9 ± 8.1 mg/L vs. 7.4 ± 12.8 mg/L) (p=0.61), indicating resolution of inflammation. These data indicate that a four-day dexamethasone regimen does not lead to prolonged secondary adrenal insufficiency.

We are the first to report serial total serum cortisol measurements during the course of disease in patients hospitalized with CAP, together with its predictive value. Our study showed that persisting higher cortisol throughout the course of CAP is associated with adverse clinical outcome. Although we have found that serial cortisol measurements can add prognostic value to other biomarkers and clinical scores for prognosis in CAP, its clinical relevance remains to be further substantiated. Δ-cortisol 0-2 or Δ-cortisol 0-4 as a biomarker has the disadvantage that the prediction of mortality/ICU admission will be delayed by 2–4 days. From that perspective, biomarkers and clinical scores that can be used on the day of presentation are to be preferred. However, Δ-cortisol might be helpful in patients without clinical improvement after the first days of treatment. No change, or even an increase in serum cortisol, is indicative of an unfavourable outcome, and might help in the decision-making to switch or extend therapy.

Previous studies that addressed the influence of corticosteroids on the HPA axis were not performed in patients with CAP, and various durations of therapy were combined for analysis, which makes extrapolation of the results to clinical practice difficult.3,7 In the present study, a fixed dexamethasone regimen was used, enabling us to determine the effects of short-term therapy more reliably.

Some limitations of our study must be named. First, our study has not been designed to study cortisol responses as a primary endpoint, and therefore cortisol was measured on day 0 and 30 at a random moment of the day. However, this did not influence our day 0 cortisol levels, because the circadian rhythm of cortisol was lost on presentation. On day 30, the time of cortisol measurement was similar for both groups. Second, recovery of the HPA axis as measured by total serum cortisol possibly paints an incomplete picture. Ideally, Synacthen tests should have been performed. Finally, patients were excluded when admitted to the ICU. We therefore could not analyze the complete course of cortisol in patients with an adverse outcome.

In conclusion, we showed that an adverse outcome of CAP was associated with persisting increased total serum cortisol levels throughout the course of disease. Delta-cortisol could be another meaningful biomarker in CAP. This finding may aid in the further development of cortisol as a biomarker for prognosis in CAP. Next, we found that adjuvant dexamethasone therapy almost completely suppressed the endogenous cortisol production after the first dose, but cortisol production was fully recovered on day 30. These findings are particularly relevant for clinical practice because adjuvant treatment
strategies in CAP are emerging, and corticosteroids appear to be a promising candidate.

Conflicts of interest statement

All authors state that they have no conflicts of interest to declare. There were no external sources of funding. There were no study sponsors involved.

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References


