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Adrenal function is related to the prognosis in moderate community-acquired pneumonia

Kolditz M[1], Halank M[1], Schulte-Hubbert B[1], and Höffken G[1]

[1] Department of Pulmonology, Medical Clinic 1, University Hospital Carl Gustav Carus, Dresden, Germany

Corresponding author:

Martin Kolditz, Department of Pulmonology, University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden, Germany, Telephone: +49-351-4584538, FAX: +49-351-4585892, Email: martin.kolditz@uniklinikum-dresden.de

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Abstract

Rationale:

The aim was to prospectively examine adrenal function including cosyntropin stimulation and its prognostic value in patients with moderate CAP.

Methods:

59 consecutive adult patients hospitalised at normal ward because of CAP were enrolled. A cosyntropin stimulation test was performed and serum concentrations of CRP, PCT, IL-6, TNFα, ACTH, cortisol, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEAS) were measured. Predefined outcome parameters were clinical instability after 72 hours, mortality and combined ICU-admission or mortality.

Results:

Critical illness related corticosteroid insufficiency (CIRCI) occurred in 6 patients (10,3%). Cortisol, age-corrected DHEA, ACTH and the DHEA/DHEAS ratio were elevated in patients remaining unstable after 72h. In multivariate analysis, cortisol (p=0.03), ACTH (p=0.04) and the PSI-score (p=0.005) independently predicted clinical instability after 72h, and only cortisol predicted mortality (p=0.04) and combined ICU-admission or mortality (p=0.006). The predictive value of serum cortisol after ROC-curve-analysis equalled that of the PSI-score. Patients with serum cortisol >734 nmol/l had a high probability for mortality (OR 38,3, p=0.002).

Conclusion:

CIRCI is rare in patients with moderate CAP. Adrenal function is related to the prognosis of CAP. The diagnostic accuracy of serum cortisol equals that of the PSI-score. Serum cortisol should be evaluated within clinical prediction scores on larger studies.

Introduction:

Concentration changes of adrenal hormones like cortisol, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEAS) have been described in patients with severe sepsis and septic shock and linked to the prognosis of the disease [1, 2]. Additionally, ratios of these hormones (DHEA/DHEAS and Cortisol/DHEA) might be associated with the development of septic shock and sepsis outcome, suggesting the importance of a balanced adrenal response to maintain an adequate inflammatory response to acute illness [1, 2].

On the other hand, the concept of critical illness related corticosteroid insufficiency (CIRCI) has been introduced. It is considered as an inadequate adrenal response to critical illness related stress together with tissue corticosteroid resistance and is characterized by an exaggerated proinflammatory response [3]. A recent consensus conference suggested, that the diagnosis is best made by a delta total serum cortisol of < 248 nmol/L after cosyntropin stimulation [3]. CIRCI was repeatedly associated with unfavourable outcome in patients with septic shock [4, 5, 3], even though therapeutic trials with low dose hydrocortisone showed conflicting results [6].

Community acquired pneumonia (CAP) is one of the predominant causes and precursors of sepsis and septic shock. Preliminary data from a small study in CAP-patients suggested a beneficial effect of low-dose hydrocortisone infusion even in the absence of septic shock, although the underlying mechanism for this effect has not been evaluated and adrenal function was not measured in that study [7].

In contrast to the possibility of CIRCI contributing to this postulated treatment effect in CAP, two recent studies found higher levels of serum cortisol to be correlated with CAP-severity and associated with nonsurvival in CAP with a predictive accuracy comparable to that of the PSI-score [8, 9]. However, in the study of Christ-Crain et al. cosyntropin stimulation had not been performed to elucidate adrenal dysfunction [8]. In the study of Gotoh et al. CIRCI was confounded by the inclusion of patients with septic shock, nevertheless it was not found to be a useful prognostic tool in their collective [9]. Neither study examined DHEA and DHEAS.

The aim of our study was to prospectively examine adrenal function including cortisol, adrenocorticotropic hormone (ACTH), DHEA and DHEAS concentrations before and after cosyntropin stimulation and their prognostic accuracy in comparison to established inflammatory parameters to predict the outcome of patients with moderate CAP. Hereby we aimed to elucidate possible diagnostic properties of these parameters as well as possible explanations of the postulated therapeutic effects of steroids in CAP without septic shock.

Methods:

59 consecutive adult patients, hospitalised between May 2007 and March 2009 for at least 24 hours at the emergency department or the normal ward because of CAP were prospectively enrolled in the study. CAP was defined as presence of a new infiltrate on chest radiography and at least one of the following: fever (≥ 38.3°C), cough, presence of purulent sputum or focal chest signs on auscultation. Patients were excluded from the study, if one of the following was present: nosocomial pneumonia, initial admission to the ICU, immunosuppression including HIV-disease or recent chemotherapy, active tuberculosis, sarcoidosis, pregnancy, concomitant medication with steroids (either acute or chronic including inhaled steroids), medication with ketoconazole or contraceptive drugs, known allergy against tetracosactid or history of adrenal, hypothalamic or pituitary disease.

The study protocol was approved by the local ethics committee. Informed consent was obtained from the participants. Disease severity was calculated according to the CRB-65-, CURB- and PSI-scores.

On the morning after hospital admission (day 1) a cosyntropin stimulation test was performed with intravenous injection 0.25mg of tetracosactrin (Synacthen®) and collection of blood samples immediately before the test and 30 and 60 minutes after injection. Concentrations of the following parameters were measured from the first blood sample directly after collection: C-reactive protein (CRP) (particle enhanced immunoturbidimetric assay, Roche Diagnostics GmbH, Mannheim, Germany, normal range < 5 mg/l), procalcitonin (PCT) (enzyme-labelled sequential chemiluminescent immunoassay [LIA], Brahms AG, Germany, normal range < 0,5 ng/ml), interleukin (IL)-6 (LIA, Siemens Medical Solutions Diagnostics, Los Angeles, USA, normal range < 2-3,5 pg/ml), tumor necrosis factor α (TNFα) (enzyme-labelled sequential LIA, Siemens Medical Solutions Diagnostics, Los Angeles, USA, normal range < 8,1 pg/ml), ACTH (two-site sequential LIA, Siemens Medical Solutions Diagnostics, Los Angeles, USA, normal range 2,6-10,1 pmol/l), and cortisol (antigen linked technique LIA, DiaSorin, Saluggia, Italy, normal range 119 – 618 nmol/l). Afterwards, aliquots of serum were stored frozen at -20^0 C, and the following parameters were analysed within 2 weeks after collection: DHEA (competitive coated tube radioimmunoassay, Diagnostic Systems Laboratories, Inc. Webster, Texas, USA) and DHEAS (competitive LIA, Siemens Medical Solutions Diagnostics, Los Angeles, USA). As normal ranges of these hormones are age- (and gender-) dependent, the percentage of age- (and sex- for DHEAS) matched normal values was

calculated as described before [2, 10]. In the blood samples collected after tetracosactrin injection, Cortisol, DHEA, DHEAS and ACTH were measured.
CIRCI was defined as a maximum difference in cortisol concentration of less than 248 nmol/l [3]. Basal cortisol levels were not included in the definition, as we felt that basal concentrations derived from septic shock patients were not appropriate for the less severely ill patients of our cohort.
Antibiotics were administered for empirical therapy as recommended by the German guideline of CAP [11].
Predefined outcome parameters were hospital- and 30-day mortality, combined hospital mortality and ICU admission, and clinical instability on day 4 (72 hours after the cosyntropin stimulation test). Clinical instability was defined as absence of one of the following criteria defining clinical stability: Heart rate $\leq$ 100/min, respiratory rate $\leq$ 24/min, systolic blood pressure $\geq$ 90 mmHg, temperature $\leq$ 37,8 ^{o}C, ability to eat, oxygen saturation $\geq$ 90%, return to baseline mental status [12].

Data of biochemical analyses are presented as median (range). Medians were compared using the non-parametric Mann-Whitney test. Receiver operating characteristic (ROC) curve analysis was used to determine the diagnostic properties of predictive parameters, optimal cutoff values were determined by Youdens index. Statistical comparisons between the areas under the curve (AUC) were calculated according to the Hanley and McNeil method [13] using MedCalc statistical software. Odds ratios were calculated by using the Mantel-Haenszel estimate. Univariate and multivariate analysis to predict the binary end points was performed by including the PSI-, CRB65- and CURB-scores and all measured serum parameters, for multivariate analyses a logistic regression model with stepwise forward selection was employed. To assess the influence of cortisol concentrations on mortality, we produced a Kaplan-Meier survival curve, comparison between the groups was done by log-rank test. A p-value of <0.05 (two-sided) was considered statistically significant. Statistical analyses were performed with SPSS version 15.0 software.

Results:

One patient was excluded from the analysis because of the final diagnosis of lung cancer instead of pneumonia. The baseline data of the other 58 patients are shown in table 1. In 21 patients (36%) a microbiological diagnosis could be established, with *S. pneumoniae* being

the predominant pathogen (38%), followed by *M. pneumoniae*, *S. aureus* and *E. coli* (14% each). Initial empirical antimicrobial therapy consisted of fluoroquinolone monotherapy in 23 (40%), betalactam monotherapy in 19 (33%), and a betalactam combined with either a macrolide in 9 (16%), a fluoroquinolone in 6 (10%) or clindamycin in 1 (2%) patients.

6 (10%) patients died in the hospital without further deaths within the 30-day-follow-up period, and 3 (5%) patients were admitted to the ICU after inclusion into the study because of deterioration of the clinical condition, who finally survived. 31 patients (53%) fulfilled all clinical stability criteria on day 4.

CIRCI occurred in 6 patients (10,3%), including one nonsurvivor. A trend was noted that more patients with CIRCI were clinically unstable after 72h (5/6 patients; OR 7,1 [95% CI: 0.78 – 65.7; p=0,082]).

As expected, the baseline cortisol level was positively correlated with ACTH (Spearman coefficient of rank correlation R=0.423; p=0.001). Moreover, cortisol levels were positively correlated with pneumonia severity as defined by the PSI-score (R=0,414; p=0.001) and with all measured inflammatory serum parameters, with the strongest association to IL-6 (R=0.523; p<0.001).

Levels of DHEA were elevated (median 167 [interquartile range 118–363] % of age-corrected normal values, p<0.001 by Wilcoxon test) in the overall cohort, whereas levels of DHEAS were not significantly different from the age- and sex-matched normal values.

Results of the measured serum parameters according to outcomes are shown in table 2. Cortisol (p<0.001), ACTH (p=0,01), age-corrected DHEA (p=0,02) and the ratio of DHEA/DHEAS (p=0,01) were significantly higher in patients who did not reach clinical stability after 72h; only cortisol was significantly higher in nonsurvivors (p=0.009) (Fig. 1).

In multivariate analysis including the three determined CAP severity scores and all measured serum parameters, only cortisol (Odds ratio 1.006 [95% Confidence interval 1.000-1.012]; p=0.03), ACTH (Odds ratio 1.346 [1.018-1.780]; p=0.04) and the PSI-score (Odds ratio 1.045 [1.013-1.078]; p=0.005) independently predicted clinical instability after 72h, and only cortisol independently predicted mortality (Odds ratio 1.002 [1.000-1.004]; p=0.04) and combined mortality or ICU-admission (Odds ratio 1.003 [1.001-1.004]; p=0.006).

The diagnostic value of serum cortisol as calculated by ROC-curve-analysis equalled that of the PSI-score for prediction of clinical instability after 72 h, mortality and combined ICU-admission or mortality and was superior to that of CRP, PCT and TNFα (table 3). Patients with a serum cortisol concentration of >734 nmol/l on day 1 had a significantly lower survival probability as documented by Kaplan-Meier-analysis (Fig. 2).

The diagnostic properties and unadjusted Odds ratios of cortisol for the prediction of clinical instability after 72h and mortality are shown in table 4.

Discussion:

The main findings of our study are, that (1) the adrenal hormones cortisol, DHEA and ACTH are related to severity and outcome of CAP, (2) CIRCI is a rare event in patients with moderate CAP, and (3) serum cortisol is superior to other serum parameters in predicting CAP outcomes and equals the prognostic accuracy of the PSI-score.

Physiologically, acute stress like severe illness leads to an activation of the hypothalamic–pituitary–adrenal axis which protects the organism against excessive inflammatory responses [14]. Studies showed an increase of cortisol levels that parallels the severity of infection and prognosis of patients with severe sepsis and septic shock [15]. Fewer studies also measured the adrenal hormones DHEA and DHEAS in sepsis. They are precursors of sex steroids, but also demonstrate immunomodulatory effects in vitro and in vivo in the context of inflammation. Thus they might play a regulatory role, partly as functional antagonists of the immunosuppressive effects of cortisol, during inflammatory processes [16, 17]. Therefore a balanced response of the adrenal hormones might be crucial for an adequate adrenal response to infections. Accordingly, studies found an increase of DHEA in patients with septic shock (but not in trauma patients), whereas DHEAS remained stable or decreased, resulting in a dissociation of DHEA / DHEAS [1, 2]. In nonsurvivors of septic shock, despite the elevation of DHEA, a dissociation of the Cortisol/DHEA ratio was seen and a prognostic relevance of this dissociation was postulated [1, 2].

Respiratory tract infections and especially CAP are a major cause of sepsis and a common precursor of the development of septic shock. To our best knowledge this is the first data reporting adrenal function including levels of DHEA and DHEAS in patients with CAP hospitalised outside the ICU. As expected, cortisol levels were positively correlated with CAP severity. Moreover, we found a positive correlation with serum inflammatory parameters, especially with IL-6. Additionally, as described in septic shock patients [1], we found elevated median age-corrected levels of DHEA in the overall cohort of our patients with moderate CAP. Moreover, when compared to patients with an uncomplicated course of the disease, we found elevated age-corrected levels of DHEA and a dissociation of DHEA and DHEAS in patients who had an unfavourable outcome. Corrected DHEA values and the

DHEA/DHEAS ratio were significantly increased in patients not reaching clinical stability after 72 h, and concordant trends were noted in patients who died. Unlike in septic shock, we did not observe a significant dissociation of cortisol and DHEA in our patients with adverse outcomes, which therefore might reflect even more advanced infection severity. However, it can be postulated that the cascade of concentration changes of adrenal hormones described in septic shock already starts in patients with moderate CAP. Whether these changes reflect adequate adrenal regulation because of more complicated disease or adrenal dysregulation resulting in a complicated infection course remains to be evaluated within larger studies.

CIRCI is frequent in patients with septic shock, occurring in up to 60%, and has been repeatedly shown to be associated with a poor prognosis [3, 4, 5]. Accordingly, a study in severe CAP-patients hospitalised on ICU found a high rate of CIRCI of 41%, however CIRCI was not associated with outcome in that study [18]. In our study, only patients initially hospitalized outside the ICU were included, and a low rate of 10% of CIRCI was noted, which probably reflects the lower disease severity. Although we found a trend towards a higher probability of remaining clinically unstable after 72h in patients with CIRCI on day 1, this difference was not statistically significant. According to our knowledge, only one other study examined CIRCI in patients with moderate CAP, but in that Japanese study on 64 patients, among patients on normal ward also patients with septic shock were included [9]. They found a comparable overall rate of 14% (9 patients including three with septic shock). No association with length of hospital stay and survival was described, however, clinical stability was not examined. Thus it might be concluded that CIRCI in patients with moderate CAP can occur, but it is a rare event of uncertain significance and might not serve as a clue for an overall major treatment effect of hydrocortisone infusion in CAP-patients without septic shock. However, the risk factors for and prognostic relevance of the rare event of CIRCI in CAP remains to be elucidated in larger studies.

Prognostic scores like the PSI-, CURB- and CRB-56-scores are important instruments in estimating the outcome of CAP-patients and thereby helpful for guiding treatment decisions. Additionally several inflammatory parameters like CRP, PCT and IL-6 have been used for the evaluation of CAP. However, continuous need for improvement of predicting the course of CAP is necessary, and serum cortisol levels have been proposed to perform excellent prognostic properties [8]. Christ-Crain et al. in their study of 278 patients with mild to severe CAP found, that serum cortisol levels are superior to CRP and PCT in predicting mortality

and have equally good prognostic accuracy as the PSI-score [8]. Other inflammatory parameters, adrenal hormones and the CRB-65- / CURB-score were not reported. Gotoh et al. in their study in 64 patients with mild to severe CAP found ACTH to be a good predictor of hospital mortality (AUC 0.818) and cortisol to be a good predictor of hospital length of stay (AUC 0.818), which on average was relatively long with 17,7 days [9]. Inflammatory serum parameters were not reported.

In our study we compared the prognostic accuracy of adrenal hormones to that of the established inflammatory serum parameters CRP, PCT, IL-6 and TNFα and three established score systems for CAP. In patients with CAP hospitalised at normal ward, because of the often low mortality rate, time to clinical stability represents another validated and less confounded outcome parameter [19, 12, 20]. It is well defined by clinical parameters and reflects a very low risk of the reoccurrence of instability or death [12]. Thus if clinical stability is reached, switch to oral antibiotics and hospital discharge can be considered [21]. We found that only ACTH, cortisol and the PSI-score independently predicted clinical instability after 72 h, and only cortisol independently predicted mortality in our cohort. As documented by ROC-curve-analysis, the accuracy of cortisol to predict clinical instability after 72 h was superior to that of other measured serum parameters and comparable to that of the difficult to calculate PSI-score. When using a cut-off of >571 mmol/l, clinical instability after 72 h of treatment was predicted with a PPV of 71%. A cut-off of > 734 mmol/l predicted mortality with a PPV of 45% and clinical instability after 72 h with a PPV of 100% and was associated with a significantly lower survival in Kaplan-Meyer analysis.

PCT is a frequently used serum parameter in assessing hospitalised patients with CAP, and various studies suggested a prognostic relevance of this parameter. However, in our cohort like in the study by Christ-Crain et al. [8], cortisol had a comparably superior prognostic accuracy than PCT (AUC mortality for cortisol: 0.827 and 0.76, respectively; for PCT: 0.60 and 0.60, respectively). Possible concepts of the interpretation of both serum parameters thus might be, that PCT predominantly has prognostic strength in defining low risk patients by low values [22, 23], as outcome parameter derived from kinetic data during treatment [24] or that it reflects a diagnostic tool able to guide decisions on antibiotic therapy [25, 8]. On the other hand serum cortisol possibly has superior strength as marker for predicting poor prognosis at hospital admission.

The main limitation of our study is the small sample size in a single institution study, for instance not allowing a clear statement regarding the prognostic relevance of and possible

predictors for the rare event of CIRCI in patients with CAP on a normal ward. Furthermore, we did not measure serum levels of free cortisol, which have been suggested to be more reliable especially in the context of critical illness related hypalbuminemia [26]. However, although serum albumin levels in our cohort were slightly lower in patients not reaching clinical stability after 72h (median levels 3,5 g/dl versus 3,9 g/dl; p=0.004), levels were not significantly different in patients who did not survive, and only 3 patients of our cohort had relevant hypalbuminemia with levels < 2,5 g/dl. Moreover, Christ-Crain et al. in their study found no difference between the prognostic values of free and total serum cortisol in a population of CAP-patients comparable to ours [8].

In conclusion, adrenal function as measured by levels of cortisol, DHEA and ACTH on hospital admission is related to severity and outcome of CAP. CIRCI is a rare event in CAP outside of the ICU, larger studies to determine its prognostic significance and risk factors are needed. Serum cortisol has a good prognostic accuracy in predicting a high risk for clinical instability after 72 h and mortality, which equals that of the difficult to calculate PSI-score. Thus, serum cortisol should be evaluated as adjunct to clinical prediction scores on larger studies.

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References:

1. Arlt W, Hammer F, Sanning P, Butcher SK, Lord JM, Allolio B, Annane D, Stewart PM. Dissociation of Serum Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate in Septic Shock. *J Clin Endocrinol Metab* 2006; 91: 2548-2554.
2. Marx C, Petros S, Bornstein SR, Weise M, Wendt M, Menschikowski M, Engelmann L, Hoffken G. Adrenocortical hormones in survivors and nonsurvivors of severe sepsis: diverse time course of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, and cortisol. *Crit Care Med* 2003; 31: 1382-1388.
3. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008; 36: 1937-1949.
4. Annane D, Maxime V, Ibrahim F, Alvarez JC, Abe E, Boudou P. Diagnosis of Adrenal Insufficiency in Severe Sepsis and Septic Shock. *Am J Respir Crit Care Med* 2006; 174: 1319-1326.
5. Lipiner-Friedman D, Sprung CL, Laterre PF, Weiss Y, Goodman SV, Vogeser M, Briegel J, Keh D, Singer M, Moreno R, Bellissant E, Annane D. Adrenal function in sepsis: the retrospective Corticus cohort study. *Crit Care Med* 2007; 35: 1012-1018.
6. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J. Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358: 111-124.
7. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della PR, Giorgio C, Blasi F, Umberger R, Meduri GU. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171: 242-248.
8. Christ-Crain M, Stolz D, Jutla S, Couppis O, Muller C, Bingisser R, Schuetz P, Tamm M, Edwards R, Muller B, Grossman AB. Free and Total Cortisol Levels as Predictors of Severity and Outcome in Community-acquired Pneumonia. *Am J Respir Crit Care Med* 2007; 176: 913-920.

9. Gotoh S, Nishimura N, Takahashi O, Shiratsuka H, Horinouchi H, Ono H, Uchiyama N, Chohnabayashi N. Adrenal function in patients with community-acquired pneumonia. *Eur Respir J* 2008; 31: 1268-1273.
10. Labrie F, Belanger A, Cusan L, Gomez JL, Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J Clin Endocrinol Metab* 1997; 82: 2396-2402.
11. Hoffken G, Lorenz J, Kern W, Welte T, Bauer T, Dalhoff K, Dietrich E, Ewig S, Gastmeier P, Grabein B, Halle E, Kolditz M, Marre R, Sitter H. [S3-guideline on ambulant acquired pneumonia and deep airway infections]. *Pneumologie* 2005; 59: 612-664.
12. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS, Singer DE. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 1998; 279: 1452-1457.
13. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983; 148: 839-843.
14. Cooper MS, Stewart PM. Corticosteroid Insufficiency in Acutely Ill Patients. *N Engl J Med* 2003; 348: 727-734.
15. Arafah BM. Hypothalamic Pituitary Adrenal Function during Critical Illness: Limitations of Current Assessment Methods. *J Clin Endocrinol Metab* 2006; 91: 3725-3745.
16. Loria RM. Beta-androstenes and resistance to viral and bacterial infections. *Neuroimmunomodulation* 2009; 16: 88-95.
17. Oberbeck R. Therapeutic implications of immune-endocrine interactions in the critically ill patients. *Curr Drug Targets Immune Endocr Metabol Disord* 2004; 4: 129-139.
18. Salluh JI, Bozza FA, Soares M, Verdeal JC, Castro-Faria-Neto HC, Lapa E Silva JR, Bozza PT. Adrenal response in severe community-acquired pneumonia: impact on outcomes and disease severity. *Chest* 2008; 134: 947-954.
19. Ramirez JA, Srinath L, Ahkee S, Huang A, Raff MJ. Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Arch Intern Med* 1995; 155: 1273-1276.
20. Menendez R, Torres A, Rodriguez dC, Zalacain R, Aspa J, Martin Villasclaras JJ, Borderias L, Benitez Moya JM, Ruiz-Manzano J, Blanquer J, Perez D, Puzo C, Sanchez-Gascon F, Gallardo J, Alvarez CJ, Molinos L. Reaching stability in

community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. *Clin Infect Dis* 2004; 39: 1783-1790.

21. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM, Jr., Musher DM, Niederman MS, Torres A, Whitney CG. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis* 2007; 44: S27-S72.
22. Kruger S, Ewig S, Marre R, Papassotiriou J, Richter K, von BH, Suttorp N, Welte T. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J* 2008; 31: 349-355.
23. Huang DT, Angus DC, Kellum JA, Pugh NA, Weissfeld LA, Struck J, Delude RL, Rosengart MR, Yealy DM. Midregional proadrenomedullin as a prognostic tool in community-acquired pneumonia. *Chest* 2009; 136: 823-831.
24. Charles PE, Tinel C, Barbar S, Aho S, Prin S, Doise JM, Olsson NO, Blettery B, Quenot JP. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. *Crit Care* 2009; 13: R38-
25. Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Muller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006; 174: 84-93.
26. Hamrahian AH, Oseni TS, Arafah BM. Measurements of Serum Free Cortisol in Critically Ill Patients. *New Engl J Med* 2004; 350: 1629-1638.

Tables:

Table 1: Characteristics of the study patients

	All patients N = 58	Survivors N = 52	Nonsurvivors N = 6
Male, No. (%)	30 (52)	29 (56)	1 (17)
Age, median (range)	72 (20 – 93)	71 (20 – 88)	79 (43 – 93)
Comorbidities, No. (%)	43 (74)	37 (71)	6 (100)
COPD, No. (%)	5 (9)	4 (8)	1 (17)
Smoking history, No. (%)	21 (36)	20 (38)	1 (17)
Antibiotic pre-treatment, No. (%)	12 (21)	10 (19)	2 (33)
Pathogen established, No. (%)	21 (36)	20 (38)	1 (17)
Bacteraemia, No. (%)	6 (10)	6 (12)	0 (0)
Length of hospital stay in days, median (range)	8 (2 – 72)	8 (2 – 72)	2,5 (2 – 6) §
Clinical stability on day 4, No. (%)	31 (53)	31 (60)	0 (0) §
CRB-65-Score, median (range)	1,5 (0 – 4)	1 (0 – 4)	2 (1 – 4)
CRB-65-Score, class (%)			
0	13 (22)	13 (100)*	0 (0)*
1	16 (28)	15 (94)*	1 (6)*
2	18 (31)	14 (78)*	4 (22)*
3	8 (14)	8 (100)*	0 (0)*
4	3 (5)	2 (67)*	1 (33)*
PSI-Score, median (range)	107 (12 – 233)	103 (12 – 184)	143 (134 – 233) §
PSI-Score, class (%)			
1	12 (21)	12 (100)*	0 (0)*
2	3 (5)	3 (100)*	0 (0)*
3	4 (7)	4 (100)*	0 (0)*
4	20 (34)	20 (100)*	0 (0)*
5	19 (33)	13 (68)*	6 (32)*
CIRCI, No. (%)	6 (10)	5 (10)	1 (17)

* Percentage of patients in risk class
§ $p < 0.05$ for nonsurvivors vs. survivors

Table 2: Laboratory parameters of the patients according to outcome

	Death			Clinically unstable on day 4		
	Yes	No	p	Yes	No	p
Leucocytes (GPt/l), median (range)	20,6 (4,0 – 46,1)	12,2 (2,2 – 49,2)	0.07	13,3 (2,2 – 49,2)	13,3 (3,6 – 25,5)	0.79
CRP, (mg/l) median (range)	200 (77 – 300)	229 (26 – 606)	0.48	220 (36 – 477)	214 (26 – 606)	0.62
PCT, (ng/ml) median (range)	1,92 (0,17 – 18)	1,29 (<0,1 – 68)	0.49	1,69 (<0,1 – 41)	0,54 (<0,1 – 68)	0.22
IL–6, (pg/ml) median (range)	76,5 (11 - >1000)	34,9 (3 - >1000)	0.13	77,5 (11 - >1000)	28,1 (3 – 177)	**0.001**
TNFα, (pg/ml) median (range)	34,2 (11 – 108)	23,6 (7 – 174)	0.34	23,9 (7 – 174)	22,8 (9 – 100)	0.34
Cortisol before ACTH (nmol/l), median (range)	986 (408 – 2208)	523 (168 – 1841)	**0.009**	685 (355 – 2208)	430 (168 – 708)	**<0.001**
Cortisol after ACTH (nmol/l), median (range)	1990 (915 – 2223)	1018 (570 – 2495)	**0.014**	1288 (586 – 2495)	950 (570 – 1523)	**<0.001**
Delta Cortisol, median (range)	676 (149 – 1274)	496 (45 – 980)	0.57	577 (45 – 1274)	477 (189 – 870)	0.25
ACTH (pmol/l), median (range)	5,9 (<2,2 – 78)	3,4 (<2,2 – 17,4)	0.12	5,1 (<2,2 – 78)	3,1 (<2,2 – 10,1)	**0.012**
DHEA (nmol/l), median (range)	47,8 (6,4 – 88)	19,7 (2,3 – 115)	0.16	23 (3,5 – 92)	19,8 (2,3 – 115)	0.38
DHEA (%)* median (range)	542 (91 – 1259)	163 (33 – 1140)	0.07	260 (50 - 1259)	139 (33 – 702)	**0.018**
DHEAS (µmol/l), median (range)	3,3 (<0,4 – 6,3)	2,6 (<0,4 – 13,3)	0,70	2,6 (<0,4 – 12,9)	3,1 (<0,4 - 13,3)	0.61
DHEAS (%)* median (range)	153 (15 – 315)	63 (8 – 370)	0.12	80 (8 - 370	63 (8 – 290)	0.44
Cortisol / DHEA, median (range)	26 (20 – 64)	31 (5 – 120)	0.96	34 (5 – 120)	20 (6 – 120)	0.13
DHEA / DHEAS, median (range)	12 (6 – 28)	8 (2 – 154)	0.08	11 (2 – 154)	7 (3 – 23)	**0.013**

* in % of age- (and sex-) matched normal value

Table 3: Receiver operating characteristic curve statistics of cortisol, established serum parameters and established severity scores for predicting clinical instability after 72 h, mortality, and combined ICU-admission or mortality

	Clinically unstable after 72h			Death			Combined ICU-admission or death		
Parameter	AUC	95%-CI	p versus cortisol	AUC	95%-CI	p versus cortisol	AUC	95%-CI	p versus cortisol
Cortisol	0.83	0.74-0.92	-	0.83	0.62-1.0	-	0.86	0.72-1.0	-
PCT	0.59	0.45-0.73	0.003	0.60	0.39-0.81	0.062	0.61	0.42-0.80	0.026
CRP	0.51	0.36-0.67	<0.001	0.42	0.22-0.63	0.026	0.48	0.28-0.69	0.002
TNFα	0.58	0.42-0.73	0.002	0.62	0.35-0.89	0.088	0.68	0.43-0.94	0.12
IL-6	0.75	0.62-0.88	0.27	0.69	0.44-0.94	0.16	0.74	0.51-0.97	0.22
PSI-score	0.85	0.75-0.95	0.8	0.86	0.75-0.97	0.86	0.82	0.70-0.94	0.75
CRB65-score	0.76	0.64-0.89	0.43	0.68	0.50-0.85	0.27	0.63	0.46-0.81	0.09

AUC = area under the curve; CI = confidence interval

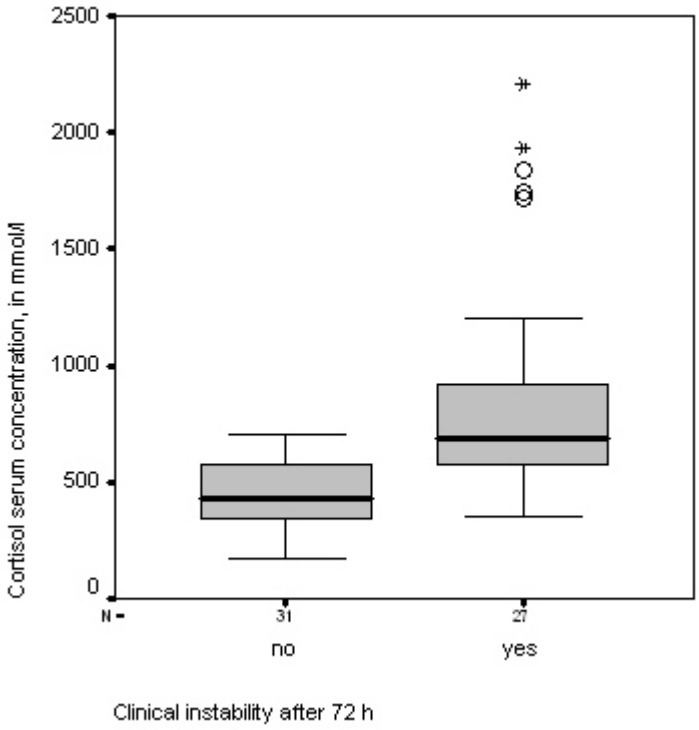
Table 4:
Odds ratios (unadjusted) and diagnostic properties of serum cortisol

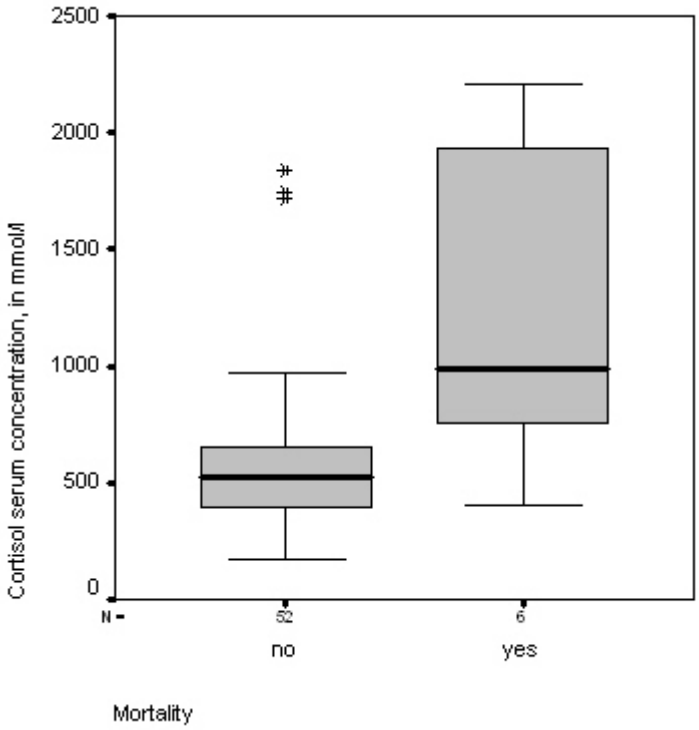
Outcome	Cortisol cut-off	Odds ratio (95%-CI)	p	Sensitivity (95%-CI)	Specificity (95%-CI)	PPV (95%-CI)	NPV (95%-CI)
Clinically un-stable after 72h	>571 nmol/l	8.2 (2.5–26.7)	<0.001	78% (58-91)	74% (55-88)	71% (51-87)	77% (58-90)
Death	>734 nmol/l	38.3 (3.8-386)	0.002	83% (36-99)	87% (74-94)	45% (17-77)	98% (89-100)

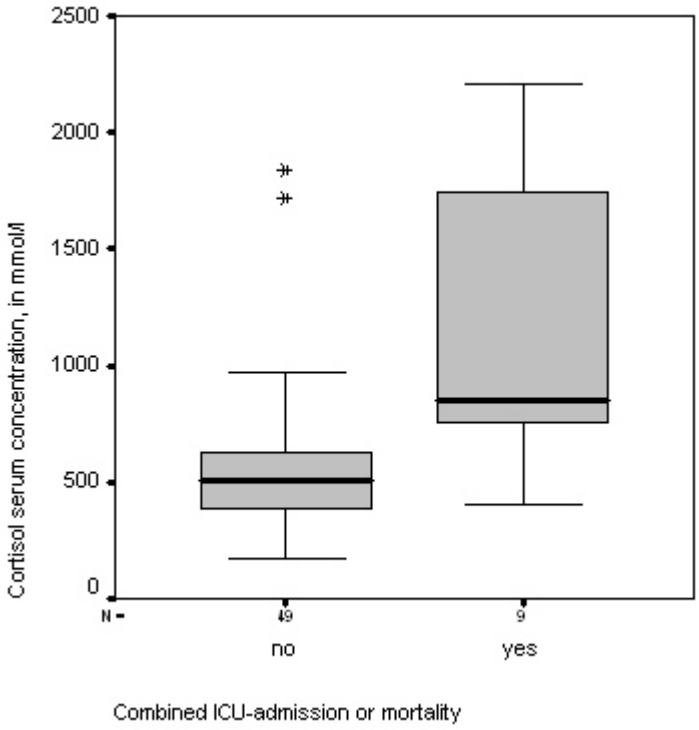
Figure legends:

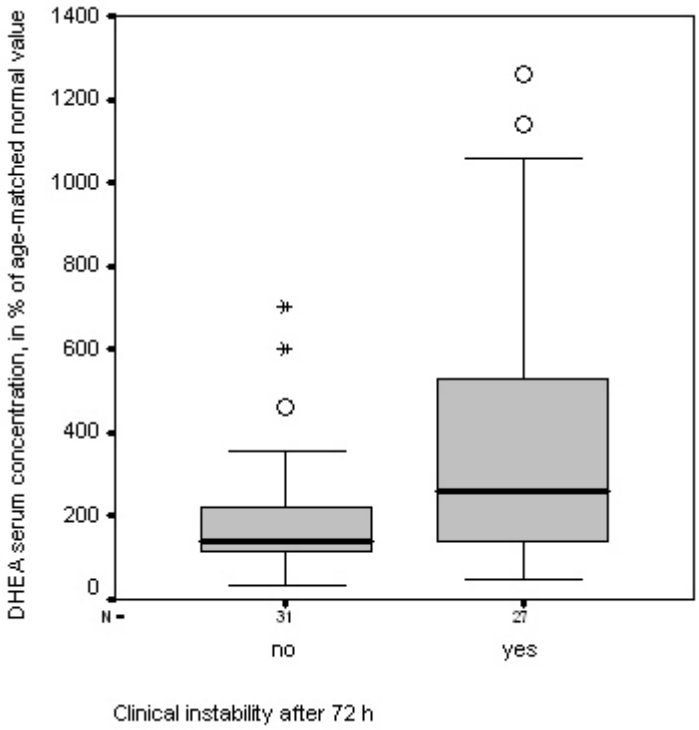
Figure 1:

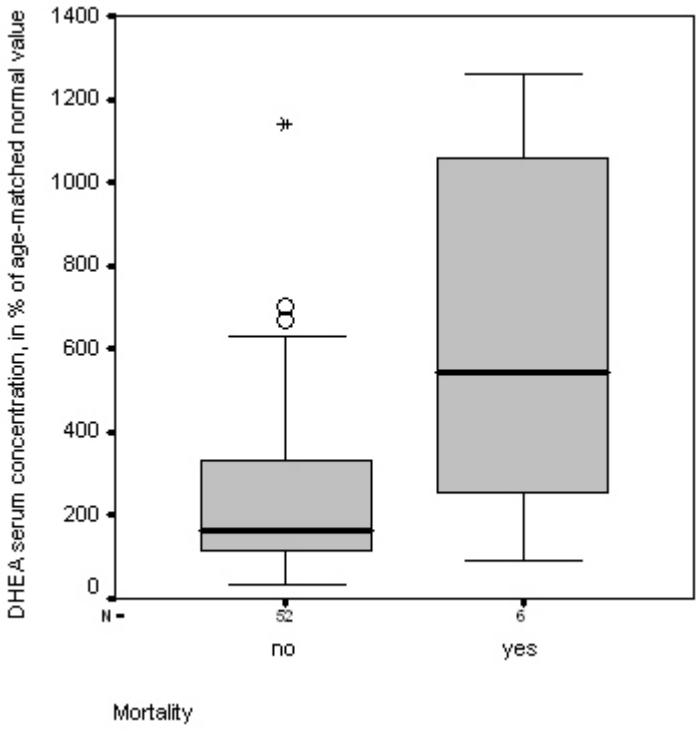
Box-plots showing serum concentrations of cortisol (a,b,c) and age-corrected DHEA (d,e,f) according to the predefined outcome parameters clinical instability after 72 h, mortality and combined ICU-admission or mortality




2500
2000
1500
1000
500
0
Cortisol serum concentration, in mmol/l
N =
52
6
no
yes
Mortality


2500
2000
1500
1000
500
0
Cortisol serum concentration, in mmol/l
N =
49
9
no
yes
Combined ICU-admission or mortality


DHEA serum concentration, in % of age-matched normal value
1400
1200
1000
800
600
400
200
0
N =
31
27
no
yes
Clinical instability after 72 h


DHEA serum concentration, in % of age-matched normal value
1400
1200
1000
800
600
400
200
0
N =
52
6
no
yes
Mortality

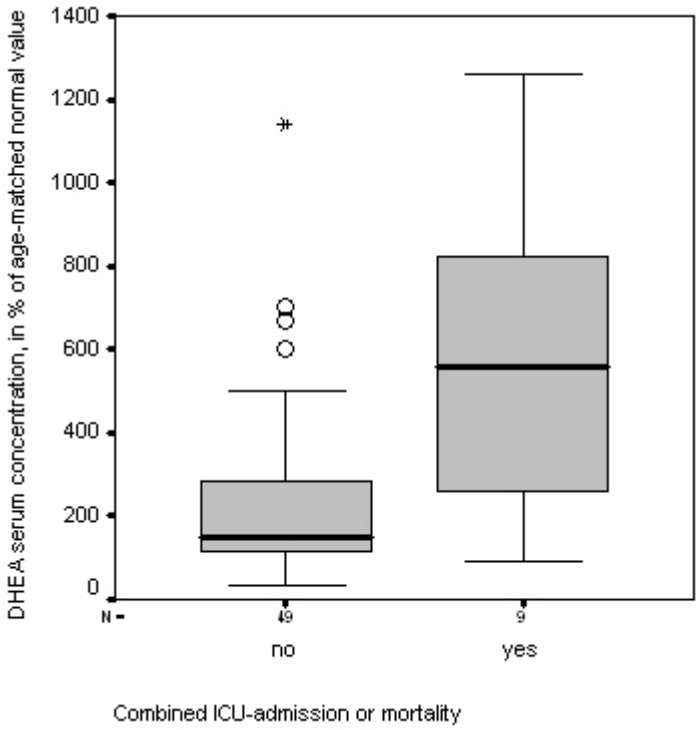
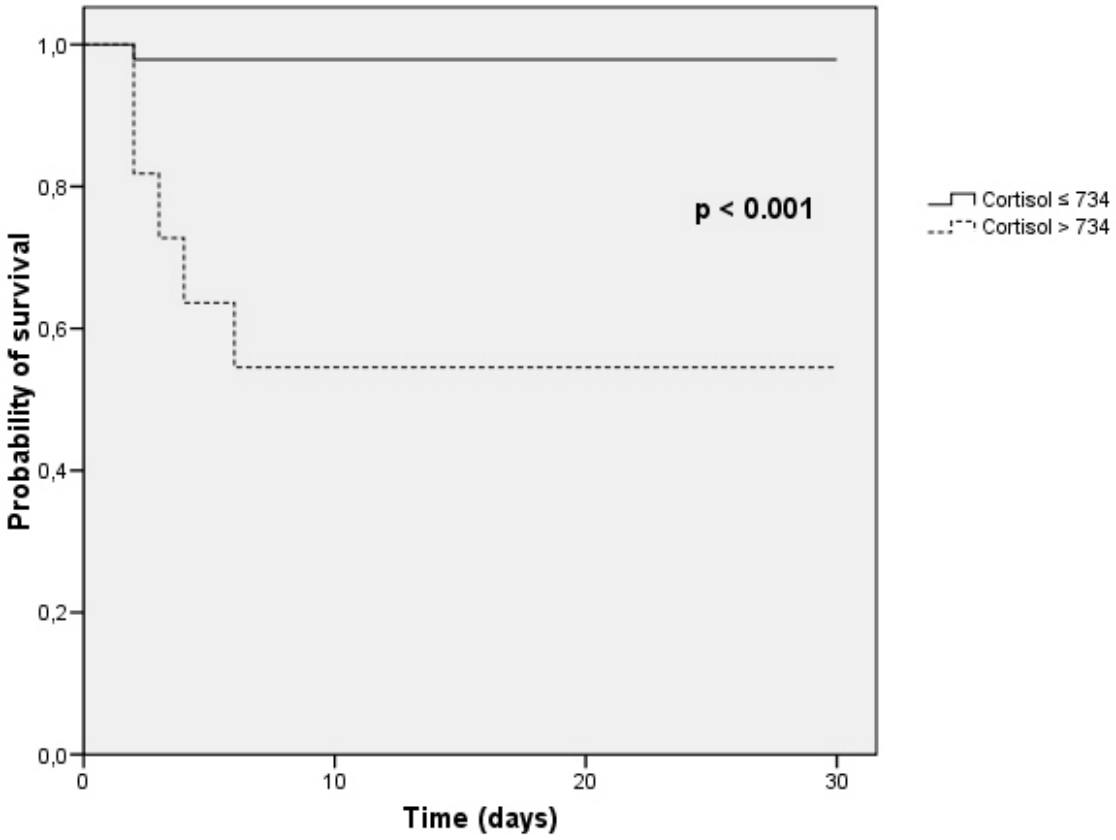


Figure 2:

Kaplan-Meier curves showing survival rates stratified by calculated optimal serum cortisol level (> 734 nmol/L). P- value determined by log rank test.


1,0
0,8
0,6
0,4
0,2
0,0
Probability of survival
p < 0.001
0
10
20
30
Time (days)
Cortisol ≤ 734
Cortisol > 734