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Cosyntropin testing does not predict response to glucocorticoids in community-acquired pneumonia in a randomized controlled trial

Short running title: ACTH testing before glucocorticoids in CAP

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SUMMARY

Objective: Glucocorticoids have been shown to improve outcome in community-acquired pneumonia (CAP). However, glucocorticoids have potential side-effects, and treatment response may vary. It is thus crucial to select patients with high likelihood to respond favorably. In critical illness, cosyntropin testing is recommended to identify patients in need for glucocorticoids. We investigated whether consyntropin testing predicts treatment response to glucocorticoids in CAP.

Design: Predefined secondary analysis of a randomized controlled trial

Patients: Hospitalized patients with CAP

Measurements: We performed 1µg cosyntropin tests in a randomized trial comparing prednisone 50mg for seven days to placebo. We investigated whether subgroups based on baseline and stimulated cortisol levels responded differently to glucocorticoids with regards to time to clinical stability (TTCS) and other outcomes by inclusion of interaction terms into statistical models.

Results: 326 patients in the prednisone and 309 patients in the placebo group were evaluated. Neither basal cortisol nor a Δcortisol<250nmol/L after stimulation nor the combination of basal cortisol and Δcortisol predicted treatment response as measured by TTCS (all p for interaction>0.05). Similarly, we found no effect modification with respect to mortality, rehospitalization, antibiotic treatment duration or CAP-related complications (all p

for interaction>0.05). However, glucocorticoids had a stronger effect on shortening length of hospital stay in patients with a baseline cortisol of ≥938 nmol/L (p for interaction=0.015).

Conclusions: Neither baseline nor stimulated cortisol after low-dose cosyntropin testing at a dose of 1 µg predicted glucocorticoid responsiveness in mild to moderate CAP. A treatment decision for or against adjunct glucocorticoids in CAP should not be made depending on cortisol values or cosyntropin testing results.

Keywords: glucocorticoids, ACTH test, cosyntropin test, adrenal function, Community-acquired Pneumonia, Critical-Illness-related Corticosteroid Insufficiency

ABBREVIATIONS

ACTH: adrenocorticotropic hormone

ARDS: acute respiratory distress syndrome

CAP: community-acquired pneumonia

CI: confidence interval

CIRCI: Critical illness – related corticosteroid insufficiency

CRP: C-reactive protein

HPA axis: hypothalamo-pituitary-adrenal axis

HR: Hazard ratio

ICU: intensive care unit

IQR: interquartile range

LOS: length of stay

PSI: pneumonia severity index

SD: standard deviation

TTCS: time to clinical stability

INTRODUCTION

There is increasing evidence that glucocorticoids improve outcome in community-acquired pneumonia (CAP) through their anti-inflammatory effects, thus attenuating the systemic inflammatory process. Two recent meta-analyses have shown that glucocorticoids significantly reduce time to clinical stability (TTCS), length of hospital stay (LOS), rates of intensive care unit (ICU) admittance and acute respiratory distress syndrome (ARDS) without an increase in complications. No significant effect on mortality was found, albeit a trend towards lower mortality.[1,2] Importantly, CAP patients are an inhomogeneous population, and it is unreasonable to assume that all of these patients would respond equally well to the same immunomodulatory agent [3]. Therefore, it is crucial to select those patients with a positive treatment response to glucocorticoids.

Severe illness activates the hypothalamo-pituitary-adrenal (HPA) axis with increased levels of cortisol.[4] In critically ill patients, there is evidence that the HPA axis is impaired in some of them, and it has been put forward that cortisol may not increase enough to cover the need to survive.[5-7] This concept was recently named critical illness-related corticosteroid insufficiency (CIRCI)[8]. With this rationale, it is recommended in critical illness to select patients in need for glucocorticoid treatment by cosyntropin testing.[8-10] For CAP outside of critical illness, no data are available investigating the predictive value of cosyntropin testing to identify patients with pronounced systemic inflammatory response who will respond to glucocorticoid treatment. We, therefore, aimed to evaluate whether cosyntropin testing identifies those patients who profit most from adjunct glucocorticoid treatment in CAP.

MATERIALS AND METHODS

Study design and participants

This is a preplanned secondary analysis of a randomized, double-blind, placebo-controlled multicenter trial comparing prednisone to placebo in patients hospitalized with CAP of any severity. Patients were recruited within 24 hours of admission in emergency departments of seven tertiary care hospitals in Switzerland from December 1, 2009, to May 21, 2014. The study details have been published elsewhere.[11] In brief, consecutive patients hospitalized with CAP were randomized upon admission to 50 mg prednisone for seven days or placebo.

The results of the main study showed a benefit of glucocorticoids in CAP.[12]

Inclusion criteria were age above 18 years and hospital admission with CAP. CAP was defined by a new infiltrate on chest radiograph and the presence of at least one of the following acute respiratory signs and one of the following symptoms: cough, sputum production, dyspnea, temperature of 38.0°C or higher, findings of abnormal breathing sounds or rales on auscultation, leucocyte count higher than 10 x 10^9/L or less than 4 x 10^9/L. Exclusion criteria were permanent inability for informed consent, active intravenous drug use, acute burn injury, gastrointestinal bleeding within the past three months, known adrenal insufficiency, a condition requiring more than 0.5mg/kg per day prednisone equivalent, pregnancy or breastfeeding, and severe immunosuppression defined as one of the following: infection with human immunodeficiency virus and a CD4 cell count below 0.35 x 10^9/L, immunosuppressive therapy after solid organ transplantation, neutropenia below 0.5 x 10^9/L , or neutrophils of 0.5 x -1 x 10^9/L during ongoing chemotherapy with an expected decrease to values below 0.5 x 10^9/L , cystic fibrosis, or active tuberculosis.

Ethics statement

The conduct of the trial adhered to the declaration of Helsinki and Good Clinical Practice Guidelines, and ethical committees of all participating hospitals (ethics committees: Ethikkommission beider Basel EKBB (Reference Number 370/08), Ethikkommission der Kantone Aargau und Solothurn (Reference Number 2011/031), commission d'ethique Lausanne (Reference Number 116/10) and Ethikkommission Bern (Reference Number 193/11)) as well as the Swiss Agency for Therapeutic Products (SWISSMEDIC (Reference Number 2009DR3227)) approved the study protocol before patient recruitment. All participants signed and received a copy of a written informed consent form before taking part in the study. The trial was registered with ClinicalTrials.gov, number NCT00973154, on 7 September 2009. It complies with the CONSORT 2010 statement.

Procedures, assays and laboratory values

After informed consent was obtained, blood was drawn and basal cortisol was measured. Then, a low-dose cosyntropin test was performed by administration of 1 µg cosyntropin. 1 microgram cosyntropin tests were performed using 0.25 mg tetracosactidum (0.250 mg/mL synthetic ACTH1–24, Synacthen©, Novartis Pharma, Switzerland) divided into 0.001mg tetracosactidum doses by the pharmacy of the University Hospital Basel (Basel, Switzerland), as described elsewhere [13,14]. After 25-30 min, blood was again drawn and stimulated cortisol was measured. Study medication was started after completion of the low-dose cosyntropin testing. Timing of cosyntropin testing was performed at time of study inclusion or, if study inclusion occurred after 8 p.m., in the next morning. In the case of delayed cosyntropin testing, the first dose of study medication was delayed as well.

Cortisol was measured by the commercially available and routinely used assay during weekdays at the corresponding study center (for assay specifications, see Table 2).

Study nurses assessed patients for clinical stability every 12 h during hospital stay. All patients were treated according to published CAP guidelines.[15]

Baseline data included medical history items, relevant comorbidities, clinical items of pneumonia, and all variables required for the calculation of the pneumonia severity index (PSI)[16]. Structured follow-up telephone interviews for secondary outcomes after discharge were done on day 30.

Endpoints

The primary endpoint TTCS was defined as time (days) until vital signs were stable for 24 h or longer. Stable vital signs were defined as a temperature of 37.8°C or lower, heart rate of 100 beats per min or lower, spontaneous respiratory rate of 24 breaths per min or lower, systolic blood pressure of 90 mm Hg or higher (≥100 mm Hg for patients diagnosed with hypertension) without vasopressor support, mental status back to level before occurrence of community-acquired pneumonia, ability for oral intake, and adequate oxygenation on room air (PaO_2 ≥60 mm Hg or pulse oximetry ≥90%). These stability criteria were based on current CAP treatment recommendations. [17] Instability was defined if at least one of these criteria were not met.

Secondary endpoints were length of hospital stay, mortality at 30 days, rehospitalization, length of total and intravenous antibiotic treatment, and incidence of complications from pneumonia (recurrence, ICU stay, rehospitalization, acute respiratory distress syndrome (ARDS), empyema, nosocomial infection, and delirium)

For both primary and secondary endpoints, we tested constellations of baseline and / or stimulated cortisol levels which have been reported [10,18,19] and proposed [8,9] to predict treatment response to glucocorticoids. This included the following constellations:

- Δcortisol < 250 nmol/L as the suggested cut-off defining an insufficient increase of cortisol after cosyntropin testing in critically ill [9,20]
- Baseline cortisol ≥ 938 and/or Δcortisol < 250 nmol/L as proposed by Annane et al. [9,18]
- Baseline cortisol ≥ 571 nmol/L and/or Δcortisol < 250 nmol/L as the median cortisol value of our studied CAP cohort [12]
- Critical illness-related corticosteroid insufficiency (CIRCI) defined as baseline cortisol < 414, as proposed by Goodman et al. [19,20]
- CIRCI defined as baseline cortisol < 275.9 and/or Δcortisol < 250 nmol/L according to the consensus statement 2008 of the American College of Critical Care Medicine [8,10]

Statistical analysis

For the analysis of adrenal function, we evaluated patients in the per-protocol population, i.e. patients fully complying with the trial protocol. For the primary endpoint, we performed Cox regression models for TTCS to compare baseline and stimulated cortisol levels between both treatment groups. Patients who died before achieving clinical stability were censored at the day of death; all surviving patients not achieving clinical stability were censored at day 30. For the primary endpoint, none of the patients was lost to follow-up. For all secondary endpoints, we calculated estimates of the effect size and corresponding 95% confidence intervals (CI) using Cox proportional hazards regression. For all time-to-event analyses of secondary endpoints, patients lost to follow-up were censored at the time of last contact; for all other analyses of secondary outcomes we used complete case analyses. To test for effect modification, we included interaction terms into the statistical models and report p values. All reported CIs are two-sided 95% intervals, and tests were done at the two-sided 5% significance level. STATA 12.1 (Stata Corp, College Station, Texas) was used for data analysis.

RESULTS

Baseline characteristics

A total of 326 patients in the prednisone group and 309 patients in the placebo group who were treated per protocol had complete cosyntropin test values and were included in this analysis (figure 1, study flow chart).

Baseline characteristics of the two treatment groups are shown in table 1. Median age of patients was 73 years, and 396 patients (62 %) were men. Patients had a high burden of comorbidities including diabetes, chronic obstructive pulmonary disease, chronic heart failure, and chronic renal insufficiency. About half the patients were in high-risk PSI classes IV and V. Baseline and stimulated cortisol levels were 573 nmol/L (402-741) and 877 nmol/L (715-1038) in the prednisone group and 563 nmol/L (389-751) and 849 nmol/L (707-1065) in the placebo group, respectively. Δcortisol upon stimulation was 295 nmol/L (188-401) in the prednisone group and 290 nmol/L (301-397) in the placebo group.

Primary endpoint

Basal plasma cortisol levels did not predict treatment response to prednisone in any of the subgroups tested with similar effects with respect to TTCS (Hazard ratios (HR) between 1.15 and 1.66, p for interaction > 0.05 for all subgroups). Similarly, neither a Δcortisol < 250 nmol/L after cosyntropin testing nor the three predefined combinations of basal cortisol and Δcortisol tested (baseline ≥ 938nmol/L and Δcortisol < 250nmol/L; baseline ≥ 571nmol/L and Δcortisol < 250nmol/L; baseline < 275.9 or Δcortisol < 250 nmol/L) predicted treatment response to glucocorticoids (p for interaction > 0.05 for all subgroups; figure 2a).

Secondary Endpoints

Basal plasma cortisol levels or Δcortisol after cosyntropin testing (whichever of the tested cutoffs used) did not predict treatment response to glucocorticoids with regards to 30-day mortality, rehospitalization, length of total or intravenous antibiotic treatment, or incidence of CAP complications (p for interaction > 0.05 for all subgroups; figures 2b to 2d and supplemental table S1 for detailed values). However, patients with a baseline cortisol value of ≥ 938 nmol/L had a significantly shorter length of hospital stay in the prednisone group as compared to the placebo group (regression coefficient -4.34 days (95% CI -8.05- -0.63) for patients with baseline cortisol ≥ 938 nmol/L, vs. -0.83 days (95% CI -1.76-0.11) for patients with baseline cortisol < 938 nmol/L; p for interaction = 0.015; figure 2b and supplemental table S2).

DISCUSSION

The main finding of our study is that - irrespective of which cutoff was used - neither baseline nor stimulated cortisol after cosyntropin testing predicted responsiveness to glucocorticoid treatment in CAP. There was only a slightly better glucocorticoid treatment effect with regards to LOS in patients with a high baseline cortisol ≥ 938 nmol/L, which might be a chance finding due to multiple testing. The “high risk” group described by Annane et al, characterized by maximal stress and a consequent basal cortisol ≥ 938 nmol/L, consisted of the most severely ill patients of a septic shock cohort.[9] Similarly, our patients with highest basal cortisol levels were more often hospitalized in the ICU, had higher PSI scores and more comorbidities as compared to the overall cohort (see also supplemental table S2). High cortisol levels have been shown to be associated with worse outcome in both sepsis and CAP.[4,7,9,21-23] Furthermore, findings of a randomized controlled study [24] and of one meta-analysis [1] suggested that patients with most severe CAP may benefit more from

glucocorticoids as compared to patients with milder CAP. Therefore, our data underline the finding that cortisol levels can serve as a surrogate marker for severity of illness.

Recent studies have contradicted the long-standing beliefs that in critical illness, ACTH levels were high in order to maintain a high cortisol production rate [6]. It has been shown that in these patients, ACTH levels are low, probably due to negative feedback by high cortisol levels, and that the cortisol response to ACTH correlates positively with cortisol production rate, i.e. a lower rise in cosyntropin testing corresponds to a lower cortisol production rate and vice versa. Furthermore, critically ill patients seem to have a slower cortisol plasma clearance. Therefore, a possible explanation for our findings showing no predictive value of the cosyntropin test is that a low response to cosyntropin testing mirrors a reduced cortisol production and suppressed cortisol breakdown but may still result in sufficient cortisol availability [6].

Recently, relatively low cortisol levels in critically ill patients, basal or after cosyntropin testing, have been termed sick euadrenal state [25], similarly to the frequently observed euthyroid sick syndrome of the thyroid [26]. The euthyroid sick syndrome represents pathophysiological adaptations of thyroid function in severe illnes rather than a situation requiring thyroid substitution. The constellation of relatively low cortisol levels or a blunted cortisol response to cosyntropin testing in critically ill patients might rather represent pathophysiological adaptations of the HPA-axis than a state in need of glucocorticoid replacement [6,20,25].

Our data showing no predictive value of cosyntropin testing for glucocorticoid responsiveness in patients with CAP underline these findings and suggest that the beneficial effect of glucocorticoids in CAP is rather due to the immunomodulatory effects of glucocorticoids than due to an effect on a presumed critical illness-related corticosteroid insufficiency (CIRCI).

Our study has the following limitations.

First, we included hospitalized patients with CAP of any severity. This led to relatively small subgroups of patients with severe CAP. Therefore, the amount of critically ill patients who potentially fulfilled the concept of CIRCI was small as compared to other studies which were conducted in the ICU setting [27,28].

Second, as a secondary subgroup analysis, even though it was preplanned, our data may be underpowered, and multiple testing in several subgroups may have increased the risk for false-positive results.

Third, the study sites used different cortisol assays, but the study sites reported a very good correlation coefficient (see also Table 2). Fourth, we performed the cosyntropin test with a low dose of 1 µg cosyntropin, which is not the standard test and is debated controversially. We therefore cannot draw conclusions about a possible predictive value of the 250 µg test in CAP. However, recent data have shown a good correlation of the 1 µg and the 250 µg cosyntropin test.[29,30] For the diagnosis of secondary adrenal insufficiency, i.e. due to inadequate ACTH secretion of the pituitary, there is even evidence that the low-dose cosyntropin test is more sensitive than the 250 µg cosyntropin test.[29,31] In critically ill patients, a few but small studies have compared the low-dose cosyntropin test to the 250 µg cosyntropin test.[30,32,33] Even though these data have shown a good correlation between the two methods, the low-dose cosyntropin test is so far not recommended to diagnose CIRCI.[8,29]

CONCLUSION

Neither baseline nor stimulated cortisol after low-dose cosyntropin testing at a dose of 1 µg predicted glucocorticoid responsiveness in mild to moderate CAP. A treatment decision for

or against adjunct glucocorticoids in CAP should not be made depending on cortisol values or cosyntropin testing results.

CONFLICTS OF INTEREST STATEMENT

We declare no competing interests in relation to this study.

AUTHOR CONTRIBUTIONS

CB, PS, MB, BM and MCC designed the study and wrote the protocol. CB, NN, BW, BA, JR, SU, MRB, NR and CB recruited patients for the study and performed cosyntropin tests. CB, PS and MCC analyzed the data and drafted the manuscript. NR, BM and MCC participated in coordination and gave financial and staff support. All authors critically revised and approved the final manuscript.

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Table 1. Baseline characteristics.

Characteristic	Prednisone group, n=326	Placebo group, n=309
Age, mean (SD), y	73 (61-83)	72 (59-82)
Male Gender, No. (%)	201 (62)	195 (63)
Clinical characteristics		
Temperature, mean (SD), °C	37.5 (37.0-38.2)	37.6 (36.9-38.3)
Systolic blood pressure, mean (SD), mmHg	124 (110-140)	125 (111-140)
Heart rate, mean (SD), bpm	84 (74-96)	83 (71-95)
Respiratory Rate, mean (SD), bpm	20 (18-24)	20 (18-24)
SaO2, mean (SD), %	94 (92-96)	95 (92-96)
Baseline data measured with oxygen administration, No. (%)	159 (49)	160 (52)
Multiple infiltrates, No. (%)	56 (17)	72 (23)
Pleural effusion, No. (%)	36 (11)	34 (11)
PSI class I-III[a], No. (%)	158 (48)	166 (54)
PSI class IV-V[a], No. (%)	168 (52)	143 (46)
Initial ICU stay	8 (2.5)	14 4.5)
- With mechanical ventilation	3 (0.9)	8 (2.6)
- With non-invasive ventilation	5 (1.5)	7 (2.3)
Comorbidities		
Diabetes mellitus, No. (%)	58 (18)	62 (20)
Chronic obstructive pulmonary disease, No. (%)	66 (20)	48 (16)
Heart failure, No. (%)	63 (19)	48 (16)
Cerebrovascular disease, No. (%)	34 (10)	24 (8)
Renal insufficiency, No. (%)	102 (31)	104 (34)
Neoplasia, No. (%)	21 (6)	19 (6)
Laboratory values		
C-reactive protein, mean (SD), mg/L	162 (84-251)	170 (74-254)
Procalcitonin, mean (SD), ng/mL	0.45 (0.17-2.29)	0.57 (0.18-3.05)
Leukocytes, mean (SD), $x10^9$/L	12.1 (8.8-15.5)	11.8 (8.7-15.6)
Adrenal function		
Baseline cortisol, mean (SD), nmol/L	573 (402-741)	563 (389-751)
Stimulated cortisol, mean (SD), nmol/L	877 (715-1038)	849 (707-1065)
Δcortisol, mean (SD), nmol/L	295 (188-401)	290 (301-397)

[a]The Pneumonia Severity Index (PSI) s a clinical prediction rule to calculate the probability of morbidity and mortality among patients with CAP. PSI risk class I: age 50 or less and no risk factors, II: < 70, III: 71-90, IV: 91-130; V: > 130 points.

Table 2. Cortisol assay according to study center.

Study center	Assay	Time range
Basel/Delémont	Immulite[a]	until May 31, 2012[b]
Basel/Delémont	Elecsys/Cobas[c]	Since November 31, 2014[b]
Aarau	Immulite[a]	entire study time
Liestal/Bruderholz	Beckman-Coulter[d]	until January 16, 2012[e]
Liestal/Bruderholz	Elecsys/Cobas[c]	Since January 17, 2012[e]
Solothurn	Beckman-Coulter[d]	Entire study time
Bern	Elecsys/Cobas[c]	Entire study time

[a] IMMULITE 2000; Siemens Medical Solution Diagnostics, Los Angeles, USA. Intra-assay coefficient of variation (CV): 5.2-7.4%. Inter-assay CV: 6.8-9.4%.

[b] in direct assay comparison at the University Hospital Basel, Switzerland with 44 patient samples, the correlation coefficient between assays was found to be very good (r = 0.974).

[c] Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannheim. Intra-assay coefficient of variation (CV): 1.0-1.7%. Inter-assay CV: 1.4-2.8%

[d] Beckman Coulter, Inc., 250 S. Kraemer Blvd., Brea, CA 92821 U.S.A. Intra-assay coefficient of variation (CV): 4.4-6.7%. Inter-assay CV: 6.4-7.9%.

[e]in direct assay comparison at the University Hospital Liestal/Bruderholz with 33 patient samples, the correlation coefficient between assays was found to be very good (r=0.9920).

FIGURE LEGENDS

Figure 1. CONSORT Study flow chart.

Figure 2a. Results for the primary endpoint.

† Cox proportional hazards model including an interaction term of the respective subgroup variable with treatment group. HR > 1 indicates a *shorter* time to clinical stability.

CIRCI1 : baseline cortisol <275.9 nmol/L or Δcortisol < 250 nmol/L

High risk constellation: baseline cortisol ≥ 938 nmol/L and Δcortisol < 250 nmol/L

Modified high risk constellation: cortisol level > 571 nmol/L (median cortisol of the studied cohort) and Δcortisol < 250 nmol/L)

Abbreviations: HR, hazard ratio; CI, confidence interval

Figure 2b. Results for length of hospital stay.

† Cox proportional hazards model including an interaction term of the respective subgroup variable with treatment group.

CIRCI1 : baseline cortisol <275.9 or Δcortisol < 250 nmol/L

High risk constellation: baseline cortisol ≥ 938 nmol/L and Δcortisol < 250 nmol/L

Modified high risk constellation: cortisol level > median of 571 nmol/L and Δcortisol < 250 nmol/L)

Abbreviations: HR, hazard ratio; CI, confidence interval

Figure 2c. Results for 30-day mortality.

† Cox proportional hazards model including an interaction term of the respective subgroup variable with treatment group.

CIRCI1 : baseline cortisol <275.9 or Δcortisol < 250 nmol/L

High risk constellation: baseline cortisol ≥ 938 nmol/L and Δcortisol < 250 nmol/L

Modified high risk constellation: cortisol level > median of 571 nmol/L and Δcortisol < 250 nmol/L)

Abbreviations: HR, hazard ratio; CI, confidence interval

Figure 2d. Results for CAP complications.

CAP complications consisted of: recurrence of pneumonia, rehospitalization, ARDS, empyema, nosocomial infections, delirium.

† Cox proportional hazards model including an interaction term of the respective subgroup variable with treatment group.

CIRCI1 : baseline cortisol <275.9 or Δcortisol < 250 nmol/L

High risk constellation: baseline cortisol ≥ 938 nmol/L and Δcortisol < 250 nmol/L

Modified high risk constellation: cortisol level > median of 571 nmol/L and Δcortisol < 250 nmol/L)

Abbreviations: HR, hazard ratio; CI, confidence interval, CAP, community-acquired pneumonia