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Efficacy of corticosteroids in community-acquired pneumonia – a randomized double blinded clinical trial

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Abstract

Background

Some studies have shown a beneficial effect of corticosteroids in patients with Community-Acquired Pneumonia (CAP), possibly by diminishing local and systemic anti-inflammatory host response.

Methods

Hospitalized patients, clinically and radiologically diagnosed with CAP using standard clinical and radiological criteria, were randomized to receive 40 mg prednisolone for 7 days or placebo, next to antibiotics. Primary outcome was clinical cure at day 7. Secondary outcomes were clinical cure at day 30, length of stay, time to clinical stability, defervescence and C-reactive protein (CRP). Disease severity was scored using CURB-65 and Pneumonia Severity Index (PSI)

Findings

We enrolled 213 patients. Fifty-four (25.4%) patients had a CURB-65 > 2 and 93 (43.7%) patients were in PSI class IV-V. Clinical cure at day 7 and 30 was 84/104 (80.8%) and 69/104 (66.3%) in the prednisolone-group, and 93/109 (85.3%) and 84/109 (77.1%) in the placebo-group (p=0.38 and p=0.08). Patients on prednisolone had faster defervescence and faster decline in serum CRP levels compared to placebo. Sub-analysis of patients with severe pneumonia did not show differences in clinical outcome. Late failure (>72 hours after admittance) was more common in the prednisolone group (20 -19.2%) than in the placebo-group(10 (6.4%), p=0.04). Adverse events were few and not different between the two groups.

Interpretation

Prednisolone (at 40 mg) once daily for a week does not improve outcome in hospitalized patients with CAP. A benefit in more severely ill patients cannot be excluded.. Because of its association with increased late failure and lack of efficacy prednisolone should not be recommended as routine adjunctive treatment in CAP.

Introduction

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality world-wide (1). Despite the developments in antibiotic therapy, no substantial progress has been made in the last decades (2). Additional therapeutic interventions next to antibiotics may help to improve outcome in patients with CAP.

Corticosteroids have been evaluated in the past decades for treatment of sepsis and septic shock. Earlier studies before 1990 showed no impact on mortality, while studies using current definitions of sepsis and septic shock showed survival benefit when corticosteroids were administered at a low dose for a prolonged period of time (3). In contrast, the CORTICUS-study failed to show mortality reduction in patients with sepsis (4). Only faster reversal of shock was observed.

Corticosteroids in CAP might be effective in reducing excess systemic and pulmonary inflammation, which might translate to improved outcome (5,6). One earlier study found a beneficial effect of hydrocortisone on the clinical course in patients with pneumococcal pneumonia (7), but a more recent study (8) showed a marked improvement in P_aO_2/FiO_2 and also a survival advantage in patients with severe CAP admitted to the ICU when treated with corticosteroids. The study was ended after inclusion of 46 patients because of the benefit found in the interim analysis. This beneficial effect of steroids on severe CAP was also found in a retrospective study (9).

Our hypothesis was that adjunctive treatment with corticosteroids next to antibiotic treatment may improve outcome in patients with CAP. We conducted a clinical randomized placebo-controlled trial in hospitalized patients with CAP. Primary end point was clinical outcome at day 7. Secondary end points were clinical outcome at day 30, length of stay (LOS), time to clinical stability (TTCS), 30 days mortality, defervescence and serum C-reactive proteine levels (CRP) .

Methods

Patients

Patients were prospectively enrolled between August 2005 and July 2008 at the Medical Centre Alkmaar, a 900-bed teaching hospital in the Netherlands. The study protocol was approved by the local medical ethics committee.

Patients were eligible if they met the following criteria: 1. Written informed consent obtained. 2. Clinical symptoms suggestive of CAP: cough (with or without sputum), fever (>38.5° C), pleuritic chest pain or dyspnoea. 3. New consolidations on chest radiograph. 4. Age 18 years or above. Patients were excluded from the study if one of the following criteria applied: Presence of severe immunosupression (HIV infection, use of immunosuppressants), malignancy, pregnancy or breastfeeding, use of macrolides for more than 24 hours, use of prednisone ≥ 15 mg for more than 24 hours, any condition requiring corticosteroids, any likely infection other than CAP, obstruction pneumonia (e.g. from lung cancer), pneumonia that developed within 8 days after hospital discharge and indications that patients were unable and/or unlikely to comprehend and/or follow the protocol. Subgroup analysis of patients with severe CAP (CURB-65 score > 2 or PSI class 4 and 5) was planned. (10,11)

Study Design

Patients were double blinded randomized to receive 40 mg of prednisolone once daily or placebo for a total of 7 days, administered in the same way as the antibiotics (IV or oral). When patients were switched from iv to oral antibiotics the study drugs was also switched. Randomisation was based on a one on one allocation by means of pre-numbered containers containing 7 vials for intravenous administrations and 7 capsules. The allocation sequence was computer generated and was kept in a safe at the hospital pharmacy throughout the course of the study.

All patients were treated with antibiotics according to national guidelines (12). In all patients urinary antigen testing for *Legionella pneumophila* was performed. In general, patients with mild to moderate severe CAP (CURB-65 < 3 or PSI I-III) were treated with amoxicillin. Patients with moderate to severe CAP, with (a suspicion of) atypical pathogens or with an intolerance to amoxicillin were started on moxifloxacin. Alteration of antibiotics treatment was allowed but the use of macrolides was discouraged because of its immunomodulating effect. Duration of antibiotic treatment was entirely left to the discretion of the medical team in charge, as was the decision whether or not to switch from IV to oral treatment. There were no criteria for hospital discharge and the investigators did not influence decisions concerning discharge.

Laboratory assessment

Standard laboratory assessment was performed on presentation and included renal and liver functions, electrolytes, glucose, haematology and CRP (Beckman Coulter Inc., Fullerton, CA, USA). Arterial blood gas analysis was performed as clinically indicated. Serum samples were drawn each day of hospitalization until day 7 and on day 14 for assessment of CRP levels.

Outcomes

Clinical outcome at day 7 and 30 was defined as: Cure—resolution or improvement of symptoms and clinical signs related to pneumonia without the need for additional or alternative therapy. Failure—persistence or progression of all signs and symptoms that developed during the acute disease episode after randomization, or the development of a new pulmonary or extra-pulmonary respiratory tract infection, or the deterioration of chest radiography after randomisation or death due to pneumonia, or the inability to complete the study owing to adverse events. Indeterminate—patients receiving less than 80% of the study drug for reasons other than clinical failure, a concomitant infection outside the respiratory tract requiring antibiotic treatment, loss to follow-up, or death unrelated to the primary diagnosis (13)

An early failure was defined as lack of resolution of signs and symptoms of pneumonia within 72 hours of treatment, and persistence or progression thereafter. A late failure was defined as a recurrence of signs and symptoms of pneumonia after 72 hours of admission following an initially beneficial response to treatment.

Time to clinical stability was assessed by using the criteria defined by Halm et al (14). In short, patients were clinically stable if all four of the following criteria were met: improvement of cough and shortness of breath, temperature below 37.8°C for at least 8 hours, white blood cell count normalizing and adequate oral intake and gastrointestinal absorption. Because of the possibility of elevated WBC by prednisolone use, the criterion of normalizing WBC was replaced by declining serum CRP levels.

Defervescence was defined as a temperature < 37.5 °C.

Microbiological investigations

At admission, a sputum specimen was ordered for Gram's stain, semi-quantative culture and *Streptococcus pneumoniae* antigen. If possible, two sets of blood cultures were drawn before the start of antibiotic therapy. Urine was collected for antigen testing for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 (enzyme immunoassay, Binax-NOW, Binax, Portland, Maine, USA). Pleural fluid if present was examined by Gram's stain, culture and *Streptococcus pneumoniae* antigen test.

Blood samples for serology (Serion ELISA classic, Virion GmbH, Würzburg, Germany) were obtained on day 1 and 14 of the study for detection of antibodies to *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, *Legionella pneumophila* serogroup 1-7, influenza A and B virus, parainfluenza virus 1-3, respiratory syncytial virus and adenovirus. A fourfold increase in antibody titer was considered as diagnostic.

Statistical Analysis

A sample size was calculated based on published data of an earlier trial (15) in which 75 patients out of a total of 220 patients with CAP received steroid treatment along with antibiotic treatment. Clinical success was 93.3% in patients with steroids and 75.9% in patients without steroids. We calculated that 92 patients were needed in both arms to detect a difference of 15% between steroid and placebo treatment at day 7 with a power of 80% and an alpha level of 0.05.

The data were summarized as frequencies or percentages for categorical variables and as means and standard deviations for continuous variables. Differences between the treatment groups were compared by the chi-square or Fisher's exact test for categorical variables and a two-sample t-test or Mann–Whitney test for continuous variables. The Kaplan-Meier method was used to analyse time from admission to discharge and TTCS. Differences in LOS and TTCS between treatment groups were compared by a log-rank test. Hazard and odds ratios are reported with 95% confidence intervals. Statistical Package for Social Sciences (SPSS®) version 16.0 was used for

data management and statistical analysis. A planned interim analysis after 125 included patients with regard to mortality, LOS and clinical outcome at day 7 and 30 showed no significant differences and the study was continued as planned.

Results

Baseline characteristics

A total of 213 patients were enrolled in the study. Mean age was 63.5 ± 18.2 years and 124 (57.9) patients were male. Study flow chart is shown in figure 1. There was an imbalance between the two study groups with respect to CRP levels on admission and prevalence of chronic heart disease (table 1). Patients with severe pneumonia were evenly distributed among the two groups (CURB-65 score ≥ 3; 28 (13.1%) versus 26 (12.2%) patients, p = 0.61; PSI 4 and 5; 48 (46.2%) versus 45 (41.3%) patients, p=0.47). Reasons for exclusion are listed in table 1 of the online supplement.

Antibiotic treatment

Antimicrobial treatment was similar in both study arms; see table 2. Twenty-six (25.0%) patients in the prednisolone group and 25 (22.%) patients in the placebo group were using antibiotics prior to admission. (online supplement, table 2)

Clinical outcome

Primary and secondary outcome parameters are shown in table 3. No differences in clinical outcome at day 7 were found between patients in the prednisolone and placebo group (80.8% versus 85.3%, p=0.38). Kaplan-Meier plots of LOS and TTCS are shown in figure 2 and 3. A total of 37 (17.4%) patients did not complete their course of study medication. Reasons for not completing the course of study medication were: death in 10 patients, overruling decisions by attending physician to prescribe corticosteroids in 14 patients (3 patients with COPD and one patient with asthma), withdrawal of informed consent in 5 patients and post randomization exclusion in 8 patients. There were no differences between the prednisolone group and the placebo group in the need for additional corticosteroids (6 (5.8%) versus 8 (7.3%) patients, p=0.64). Of the 14 patients who were given additional corticosteroids, 7 (50.0%) were admitted to

the ICU. Resolution of fever was faster in the prednisolone group (figure 4). Median (±interquartile range (IQR)) day of defervescence was 2±1 days in the prednisolone group and 3±2 days in the placebo group (p<0.01).

The decline in CRP-levels was faster in the prednisolone group up until day 7 (figure 5). At day 14, patients in the prednisolone group had higher CRP levels compared to patients in the placebo group (41.73±64.98 versus 22.05±53.32 mg/l, p<0.01).

In patients with non-severe CAP late failures occurred more often in the prednisolone group than in the placebo group (CURB-65 0-2; 15/76 versus 5/87 patients, p<0.01 and PSI classe I-III; 10/56 versus 4/64 patients, p=0.05).

In the prednisolone group, 5 (4.8%) patients with late failure needed an additional course of antibiotics, 7 (6.7%) patients needed another or a prolonged course of prednisolone and 6 (5.8%) patients developed a pleural effusion or empyema necessitating additional therapy. In the placebo group, 2 (1.8%) patients needed additional antibiotics, 3 (2.8%) patients needed a course of prednisolone and 1 patient developed a pleural effusion requiring additional therapy.

Sub analysis of primary and secondary outcomes parameters in patients with severe CAP (CURB-65 > 2 or PSI class 4 and 5) are shown in table 4. Sub analysis of mechanical ventilated patients showed no differences in the primary and secondary outcome parameters (online supplement, table 3).

Etiology

An etiological diagnosis for CAP was made in 118 (55.4%) patients; *S. pneumoniae* (78 (36.6%) was the most frequently found causative micro-organism. Distribution of the pathogens between the two groups is shown in table 5. Patients with pneumococcal pneumonia in the prednisolone group had a lower clinical cure rate than patients with pneumococcal pneumonia in the placebo group. The clinical cure rate in the prednisolone group at day 7 and day 30 was 29 (69.0%) and 20 (47.6%). In the placebo group the clinical cure rate was 31(86.1%) and 28 (77.8%) (p=0.08 and p=0.01). Patients with pneumococcal pneumonia and prednisolone treatment also had a significantly higher number of late failures (11 (26.2%) versus 2 (5.6%), p=0.02). Patients in the prednisolone group who had no pathogen identified had a shorter TTCS than patients in the

placebo group (3 (IQR 2) versus 4 (IQR 2) days, p=0.01), a shorter LOS (5.5 (IQR 3) versus 7 (IQR 7) days, p=0.03) and faster defervescence (2 (IQR 1) versus 3 (IQR 3), p<0.01). No other differences were observed with respect to etiology and clinical outcome.

Adverse events

Hyperglycemia with the need for additional therapy during admission occurred in 5 (2.3%) patients in the prednisolone group and 2 (0.9%) patients in the placebo group (p=0.27). Confusion during admission was noted in 4 (1.9%) patients in the prednisolone group and in 3 (1.4%) patients in the placebo group (p=0.72). A superinfection occurred in 10 (2.1%) patients in the prednisolone group and in 4 (1.9%) patients in the placebo group (p=0.10). One patient in the placebo group developed a fungal infection after he was treated with hydrocortisone for septic shock in the ICU after clinical failure. Another patient in the placebo group was diagnosed with pulmonary embolism after 10 days hospital admission. A total of 63 (60.6%) patients in the prednisolone group and 72 (66.1%) in the placebo group did not have any treatment related adverse event (p=0.41).

Discussion

This is the first randomized double-blinded placebo controlled trial of corticosteroids in hospitalized patients with CAP. We found no beneficial effects of adjunctive corticosteroids in patients hospitalized with CAP; clinical cure was equal in both groups at day 7. A trend towards a higher clinical cure rate in the placebo group was observed. The overall clinical cure rate - 83% at day 7, and 71.8% at day 30 – is in concordance with other studies (15). Our findings contrast with the findings in other recent studies. In experimental studies a benefit has been found with the combination of hydrocortisone and antibiotics (16,17). Both studies demonstrated a reduction in inflammatory cytokines. The use of ciprofloxacin and hydrocortisone in a piglet model of Pseudomonas pneumonia also decreased bacterial burden more than ciprofloxacin treated or untreated piglets. In the only randomized double-blinded clinical trial published to date, evaluating corticosteroids in patients with CAP admitted to the ICU, a marked reduction in mortality and LOS was found (8). The study included a small number of patients because the study was ended after

interim analysis showed reduced mortality and improved oxygenation in patients treated with corticosteroids. A Spanish retrospective study also found a reduced mortality in patients treated with corticosteroids (9). Both these studies only included patients with severe CAP, who are more likely to benefit from corticosteroids. A possible rationale for the use of corticosteroids is the existence of relative adrenal insufficiency in severe CAP (18). However, patients included in the CORTICUS study had sepsis or septic shock, with one third of the patients suffering from a pulmonary infection (4). There were no better outcomes in patients who were non responders to a corticotrophin test. In our study, sub analysis of patients with severe CAP did not show a beneficial effect of corticosteroids, although our definition of severe CAP was based on the CURB-65 or the PSI, not the modified American Thoracic Society criteria as used by Confalonieri et al.(8,19). Also the absolute numbers of patients who needed mechanical ventilation was low. Gotoh et al. (20) examined adrenal insufficiency in 64 patients hospitalized with CAP and found a low incidence of adrenal insufficiency in these population. Only 14 percent fulfilled the criteria for adrenal insufficiency. Adrenal insufficiency is probably not clinical relevant in patients with non severe CAP.

Symptom resolution, reduction of LOS and reduction of intravenous antibiotic therapy are also important clinical goals in the treatment of patients with CAP. In a study by Mikame et al. (21), the authors concluded that corticosteroids in patients with CAP hastens symptom resolution and shortens the duration of treatment with intravenous antibiotics. No effect on LOS was observed, but this study suffered from a low number of included patients and the open label design. The anti-inflammatory effects of prednisolone did not lead to a shorter LOS or TTCS in our study, despite the observed faster defervescence and decline in CRP in patients treated with prednisolone. The more than twofold increase of late failures in the prednisolone group raises questions about the occurrence of a rebound of inflammation after initial suppression by corticosteroids. Subclinical inflammation is found in a majority of patients with severe CAP.In a large study elevated IL-6 levels were found in clinical stable patients with severe CAP on the day of discharge. Furthermore, higher IL-6 levels were correlated with a higher mortality in the subsequent 3 months (22). The assumption of rebound of inflammation in our study is strengthened by the higher CRP levels in patients in the prednisolone group after 2 weeks, following an initially faster decline in the first

week. This rebound phenomenon is also observed in the study by Garcia-Vidal et al. (9). Non-survivors on corticosteroid therapy died later than non-survivors without corticosteroids, respectively 13.8 versus 7.1 days. The effect of a delayed inflammatory response due to withdrawal of corticosteroids can cause a prolongation of the time between admission and death in the non-survivors with corticosteroids. In light of the presence of subclinical inflammation in patients with CAP on hospital discharge a tapering of corticosteroids might protect patients against the rebound of inflammation (22). Another possible explanation for the higher incidence of late failure may be nosocomial infection, leading to additional treatment. Nevertheless, similar to this trial, recent meta-analysis found no evidence of increased risk for nosocomial infections in corticosteroid-treated patients (3). In our study, the inclusion of patients with non severe pneumonia may have resulted in a higher rate of late failures instead of increased late mortality. Late failures may lead to new or prolonged courses of antibiotics or corticosteroids and subsequently to a higher risk of adverse events. The corticosteroid treatment-related adverse events in our study, however, were low and did not differ from placebo. The time to clinical stability was similar between the two groups, with a mean of 5 days. As the TTCS can be used as a decision tool for safely switching antibiotics from intravenous to oral administration, the effect of prednisolone on the duration of intravenous antibiotic therapy will be limited (23). CAP can be caused by different pathogens and the effect of prednisolone on the different pathogens can also be different. Patients with pneumococcal pneumonia treated with corticosteroids had a higher clinical failure rate in our study. No effects on outcome with respect to other pathogens were noted, although the absolute numbers in our study may have been be too small to detect such differences.

Some limitations may apply to our study. First, no assessment of adrenal function was performed in these patients, so no data regarding the presence of relative adrenal insufficiency are known. Secondly, the use of clinical cure as primary outcome is a subjective outcome parameter, prone to bias. But in our opinion this reflects daily clinical practice and because of the randomized design the introduction of bias is minimized.

Furthermore the exclusion criteria of the need for corticosteroid therapy may have led to an under-representation of patients with COPD. The simultaneous occurrence of bronchial obstruction and

CAP in patients with COPD necessitates the use of systemic corticosteroids in these patients (24). Although the question of whether mortality by CAP is higher in patients with COPD is still a subject for debate, the possible exclusion of these patients may have created a selection bias (25,26). The percentage of patients with COPD in our study was 20.2%, while in a previous study in our hospital 36.6% of the patients with CAP had COPD (15). Our findings should not be extended to patients with CAP and COPD, as generalizability is limited.

A fourth possible limitation is that our study may have been underpowered to detect a clinically significant difference in this population, which also included a large proportion of non severe pneumonia. But even in this case, the number needed to treat to detect a favourable outcome with prednisolone will not be clinically relevant. Also the effect of prednisolone can be diminished by a late administration. As the clinical cure rate is rather high in non severe pneumonia, the administration of prednisolone 24 hours after admission is not likely to have a significant effect on the clinical course. As all patients were included within 24 hours of admission, we do not think this limits our findings.

The Dutch guidelines concerning antibiotic therapy in patients with CAP differ from the IDSA/ATS guidelines (12,27). The low antibiotic resistance in the Netherlands (see http://www.swab.nl/swab/cms3.nsf/nethmap2009-04/$file/h4.htm) and the conflicting data in the literature concerning combination therapy supports the antibiotics used in this study conducted in the Netherlands (28, 29)

And as a last limitation we used prednisolone in a once daily dosage, for practical reasons, which may not be sufficient for establishing effective serum levels during 24 hours although the pharmacodymanic effects are known to last beyond the time frame indicated by pharmacokinetic parameters. This limits the comparison with studies using hydrocortisone by continuous infusion.

In conclusion,prednisolone at 40 mg once daily for one week does not improve outcome in hospitalized patients with CAP. A benefit in more severely ill patients cannot be excluded, Because of its association with increased late failure in patients with non-severe CAP and lack of benefit prednisolone should not be recommended as routine adjunct treatment in CAP.

Contributors

DS, JD, CG and WB contributed to the study design and the study protocol, DS and WB conducted the study. All authors contributed to the analysis of the data and preparing of the manuscript.

All authors have nothing to declare.

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Some of the results of these studies have been previously reported in the form of an abstract at the 2009 annual ATS conference (30)..

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Figure 1. Study flow chart

Figure 2.Kaplan-Meier curves showing the effect of the intervention on length of stay in the intention-to-treat population. Log rank 0.84, hazard ratio 1.15; 95% CI, 0.81-1.55, p=0.36.

Figure 3.Kaplan-Meier curves showing the effect of the intervention on time to clinical stability (TTCS) in the intention-to-treat population. Log rank 0.60, hazard ratio 1.14; 95% CI; 0.82-1.59, p=0.44.

Figure 4. Defervescence in patients with CAP treated with prednisolone or placebo.

Data are presented as mean±SD. * $p<0.01$.

Figure 5. Serum CRP-levels during treatment and at day 14 for patients in both study groups.

Data are presented as mean±SD. * $p=0.03$, ϕ $p<0.01$.

Table 1. Demographic features of the intention to treat group of hospitalized patients with CAP (213 patients).

	Prednisolone group (n=104)	**Placebo group (n=109)**	**p-value**
Age - yrs	63.0 ± 17.9	64.0 ± 18.7	0.67
Male gender	55 (52.9)	69 (63.3)	0.12
Current smoker	28 (26.9)	38 (34.9)	0.21
Never smoker	27 (26.0)	22 (20.2)	0.32
Comorbidities			
COPD	19 (18.4)	24 (22.0)	0.52
Asthma	8 (7.9)	10 (9.5)	0.68
Diabetes mellitus	10 (9.6)	12 (11.0)	0.74
Neurological disease	7 (6.8)	11 (10.1)	0.39
Chronic heart disease	10 (9.7)	24 (22.2)	0.01
Ischemic heart disease	14 (13.6%)	22 (20.2)	0.20
Clinical signs and symptoms			
Temperature - ° C	38.3 ± 1.2	38.5 ± 1.0	0.19
Systolic blood pressure - mmHg	127.8 ± 24.1	129.3 ± 24.5	0.65
Heart rate - bpm	100.6 ± 20.6	97.0 ± 18.7	0.18
Respiratory rate - /min	26.5 ± 7.4	25.5 ± 7.2	0.29
C-reactive protein - mg/l	258.5 ± 154.0	214.5 ± 144.2	0.03
WBC – x 10^9/l	14.8 ± 6.8	15.3 ± 7.2	0.58
ICU admission	15 (14.4)	7 (6.4)	0.06
CURB-65			
Score 0	18 (17.3)	26 (23.9)	0.24
Score 1	33 (31.7)	25 (22.9)	0.15
Score 2	25 (24.0)	32 (29.4)	0.38
Score 3	18 (17.3)	17 (15.6)	0.74
Score 4	9 (8.7)	9 (8.3)	0.92
Score 5	1 (1.0)	0	
Pneumonia Severity Index			
Class 1	16 (15.4)	12 (11.0)	0.35
Class 2	22 (21.2)	21 (19.3)	0.73
Class 3	18 (17.3)	31 (28.4)	0.05
Class 4	35 (33.7)	28 (25.7)	0.20
Class 5	13 (12.5)	17 (15.6)	0.52

Data are presented as n (%) or mean ± SD. COPD: chronic obstructive pulmonary disease; WBC: white blood cell count; ICU: intensive care unit.

Table 2: Antimicrobial treatment in the two study groups

	Prednisolone group	**Placebo group**	**p-value**
Amoxicillin	58 (55.8)	64 (58.7)	0.66
Moxifloxacin	42 (40.4)	38 (34.9)	0.41
Amoxicillin/clavulanic acid	4 (3.8)	5 (4.6)	0.79
Amoxicillin and acyclovir	0	1 (0.9)	
Ciprofloxacin and cefuroxime	0	1 (0.9)	

Data are presented as n(%).

Table 3. Clinical outcome by intention-to-treat and per protocol analysis.

Outcome	Prednisolone group	Placebo group	p-value	Odds ratio or mean difference (95% CI)
Intention to treat				
Clinical cure at day 7	84/104 (80.8)	93/109 (85.3)	0.38	0.72 (0.35-1.49)
Clinical cure at day 30	69/104 (66.3)	84/109 (77.1)	0.08	0.59 (0.32-1.07)
30 day mortality	6/104 (5.8)	6/109 (5.5)	0.93	1.05 (0.33-3.37)
LOS - days	10.0 ± 12.0	10.6 ± 12.8	0.16	-0.56 (-4.00-2.8)
TTCS – days	4.9 ± 6.8	4.9 ± 5.2	0.97	0.03 (-1.6-1.71)
Early failure	14/104 (13.5)	14/109 (12.8)	0.89	1.06 (0.48-2.33)
Late failure	20/104 (19.2)	10/109 (9.2)	0.04	2.36 (1.05-5.31)
Per protocol				
Clinical cure at day 7	79/97 (81.4)	87/102 (85.3)	0.47	0.76 (0.36-1.60)
Clinical cure at day 30	65/97 (67.0)	79/102 (77.5)	0.10	0.59 (0.36-1.11)
30 day mortality	6/97 (6.2)	6/102 (5.9)	0.93	1.06 (0.33-3.39)
LOS - days	10.0 ± 12.1	10.4 ± 13.1	0.83	-0.40 (-4.01-3.22)
TTCS – days	5.0 ± 7.0	4.9 ± 5.3	0.90	0.12 (-1.68-1.92)
Early failure	13/97 (13.4)	13/102 (12.7)	0.89	1.06 (0.47-2.42)
Late failure	18/97 (18.6)	9/102 (8.8)	0.05	2.35 (1.00-5.53)

All data are presented as n (%) or mean±sd. LOS: length of stay; TTCS: time to clinical stability.

Table 4. Sub analysis of clinical outcome of severe pneumonia as defined by CURB-65 score > 2 or PSI class > 3 by intention to treat analysis.

	Prednisolone group	**Placebo group**	**p-value**	**Odds ratio or mean difference (95% CI)**
CURB-65 3-5				
Clinical cure at day 7	15/28 (53.6)	15/26 (57.7)	0.76	0.85 (0.29-2.48)
Clinical cure at day 30	13/28 (46.4)	10/26 (38.5)	0.55	1.39 (0.47-4.10)
30 day mortality	4/48 (14.3)	3/45 (11.5)	0.76	1.28 (0.26 – 6.35)
LOS - days	19.4 ± 20.2	20.4 ± 22.7	0.87	-1.00 (-13.24-11.24)
TTCS -days	9.9 ± 11.2	8.7 ± 9.8	0.72	1.13 (-5.18-7.43)
Early failure	10/28 (35.7)	10/26 (38.5)	0.84	0.89 (0.94-2.69)
Late failure	5/28 (17.9)	5/26 (19.2)	0.30	0.91 (0.23-3.61)
Pneumonia severity index classe 4-5				
Clinical cure at day 7	31/48 (64.7)	32/45 (71.1)	0.50	0.74 (0.31 – 1.77)
Clinical cure at day 30	24/48 (50.0)	26/45 (57.8)	0.45	0.73 (0.32 - 1.66)
30 day mortality	5/48 (10.4)	5/45 (11.1)	0.91	0.93 (0.25 – 3.46)
LOS - days	15.0 ± 16.4	16.4 ± 18.4	0.71	-1.38 (-8.85 - 6.09)
TTCS -days	7.7 ± 9.8	6.8 ± 7.6	0.68	1.96 (-3.07 – 4.71
Early failure	13/48 (27.1)	12/45 (26.7)	0.96	1.02 (0.41 - 2.56)
Late failure	10/48 (20.8)	6/45 (13.3)	0.34	1.71 (0.57 - 5.17)

All data are presented as n (%) or mean±sd. LOS: length of stay; TTCS: time to clinical stability.

Table 5. Aetiology of 231 patients with CAP.

	Prednisolone group (n=104)	**Placebo group (n=109)**
S. pneumoniae	42 (40.4)	36 (33.0)
M. pneumoniae	7 (6.7)*	7 (6.4)
L. pneumophila	1 (1.0)	7 (6.4)
Gram negative bacteria	4 (3.8)	4 (3.7)
Staphylococcus aureus	2 (1.9)	0
Streptococcus intermedius	0	1 (1.0)
Influenza A/B	5 §	1 (1.0)
Adenovirus	2 (1.9)	1 (1.0) §§
No pathogen	45 (43.3)	50 (45.9)

Data are presented as n (%).
*Mixed infection with *S.pneumoniae*
§ 1 Mixed infection Influenza A/*H. influenza*e, 2 mixed infection Influenza A/*S. pneumoniae*
§§1 mixed infection *M. pneumoniae*/*S. pneumoniae*

Figure 1. Study flow chart

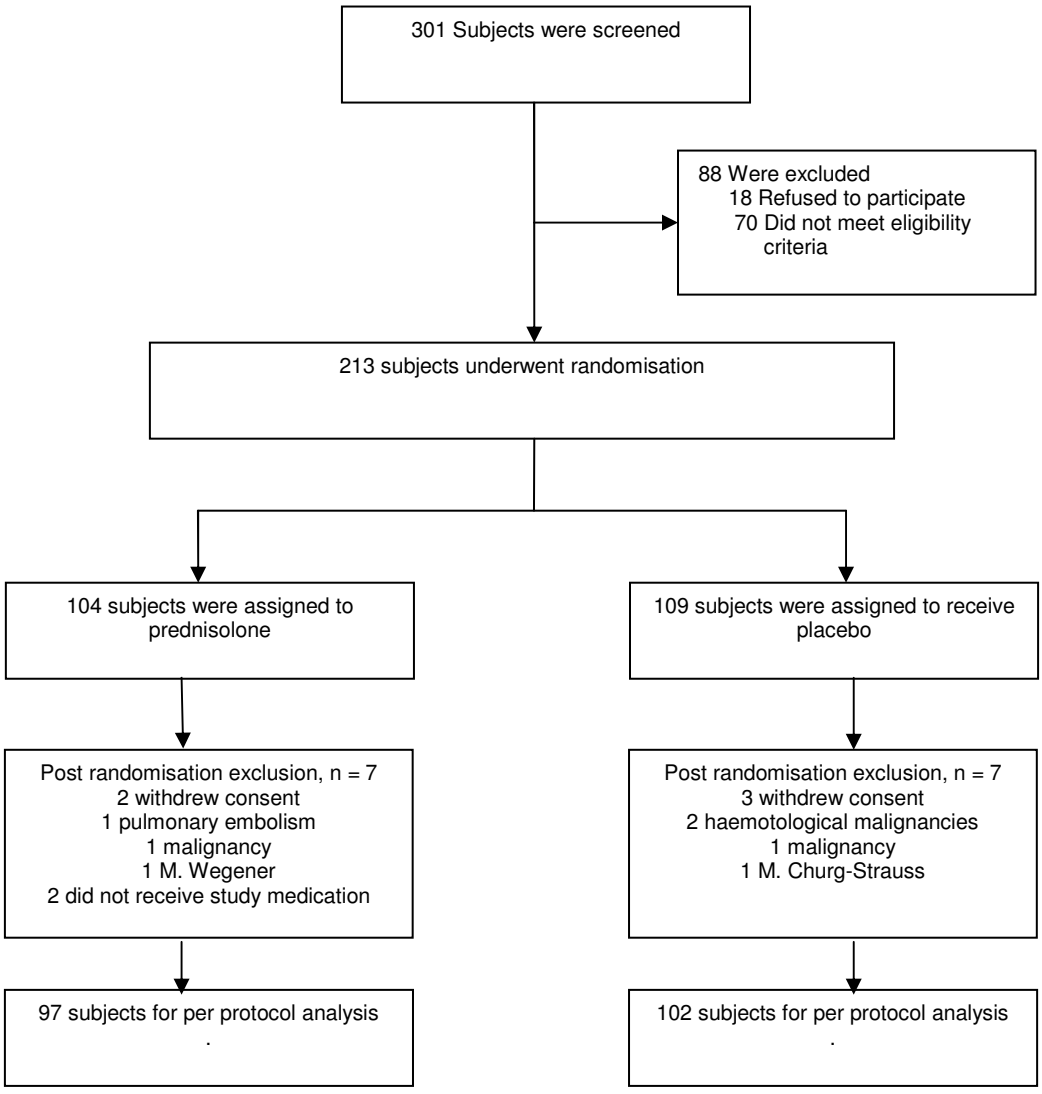


Figure 2. Kaplan-Meier curves showing the effect of the intervention on length of stay in the intention-to-treat population. Log rank 0.84, hazard ratio 1.15; 95% CI, 0.81-1.55, p=0.36.

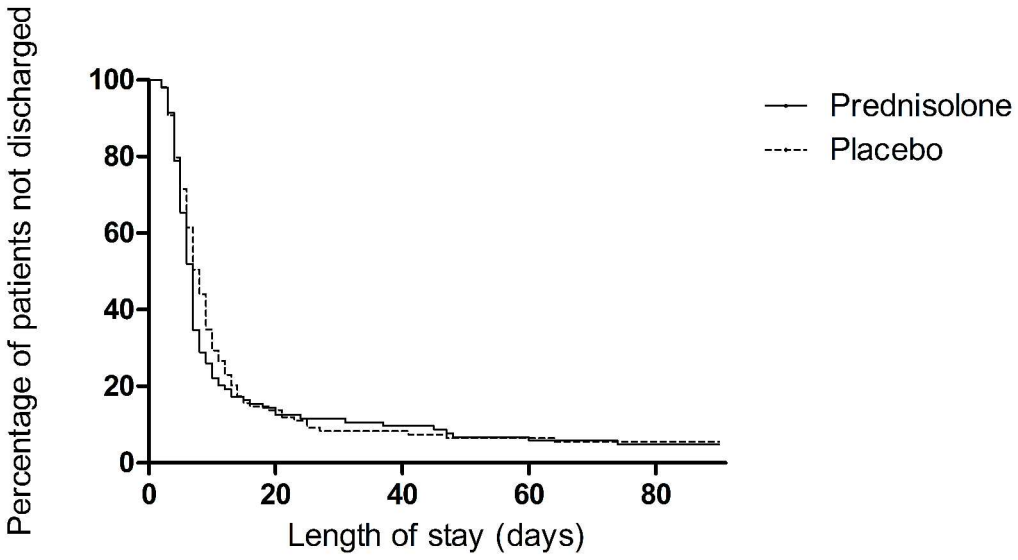


Figure 3. Kaplan-Meier curves showing the effect of the intervention on time to clinical stability (TTCS) in the intention-to-treat population. Log rank 0.60, hazard ratio 1.14; 95% CI; 0.82-1.59, p=0.44.

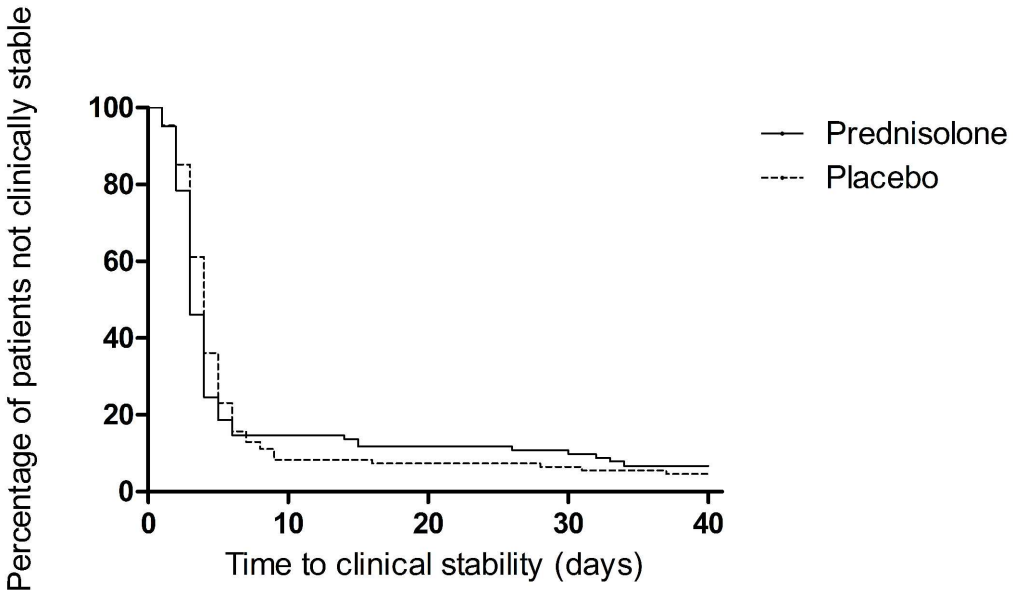
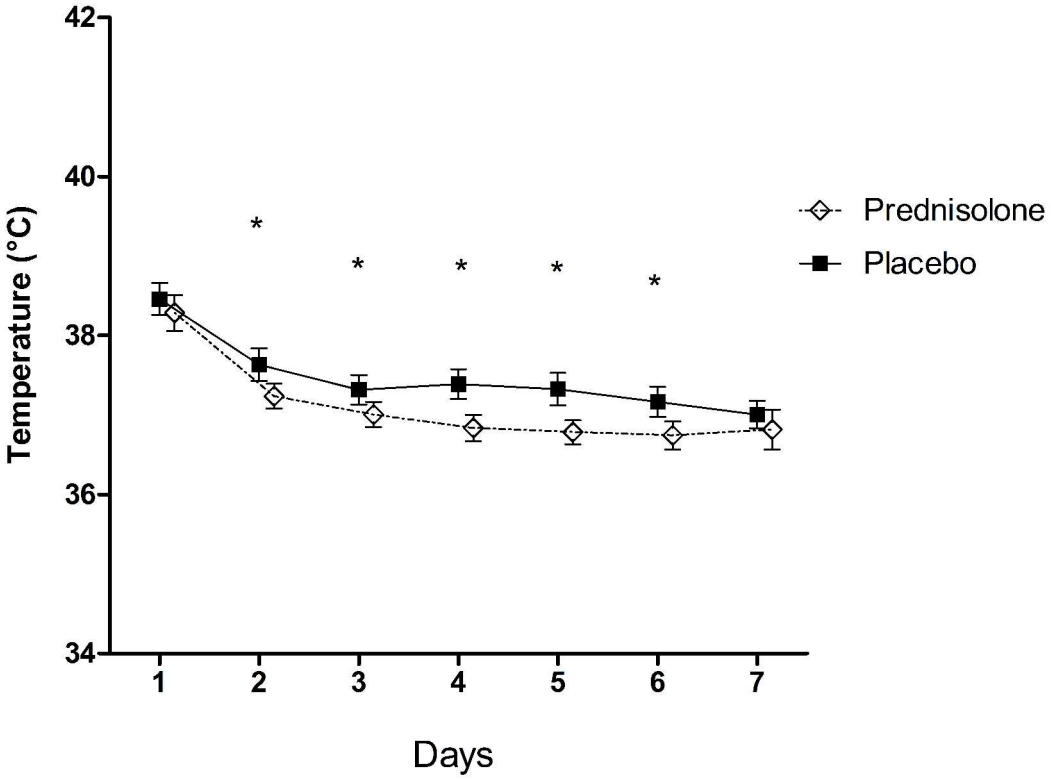
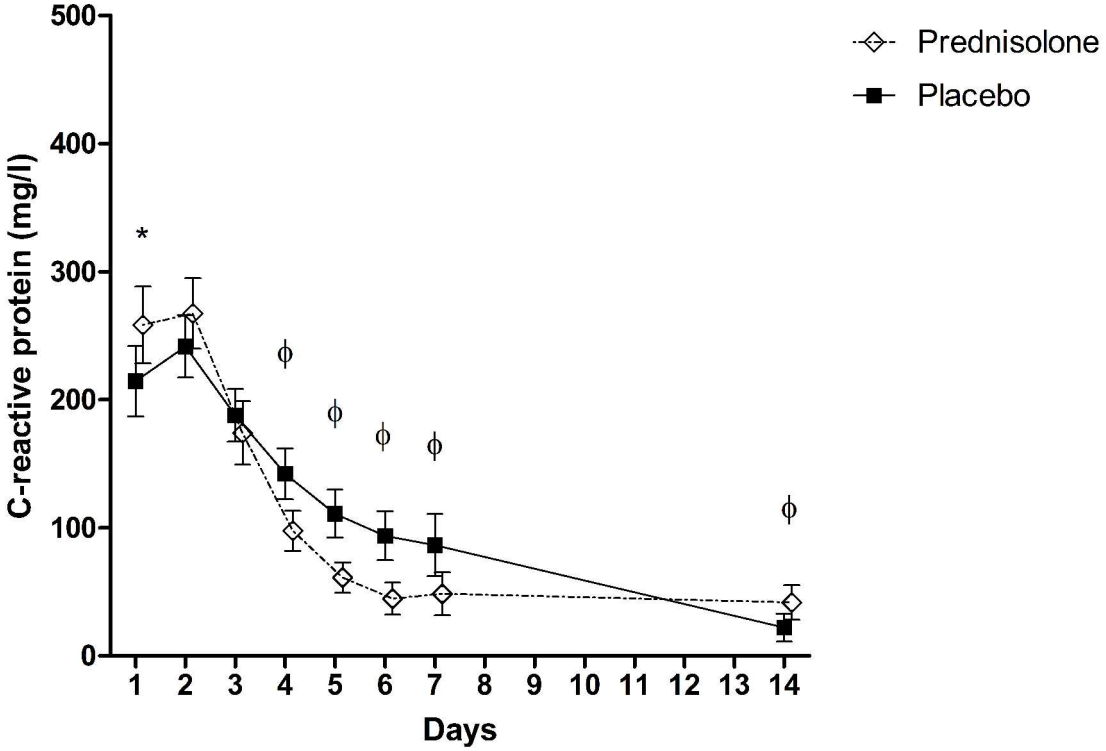


Figure 4. Defervescence in patients with CAP treated with prednisolone or placebo.



Data are presented as mean±SD.* p<0.01.

Figure 5. Serum CRP-levels during treatment and at day 14 for patients in both study groups.



Data are presented as mean±SD. * p=0.03, ϕ p<0.01.

Efficacy of corticosteroids in community-acquired pneumonia – a randomized double blinded clinical trial

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Online Data Supplement

Table E1. Reasons for exclusion in patients screened

88 patients excluded	20 (22.7%) no informed consent	
	68 (77.3%) did not meet inclusion criteria	24 no inclusion within 24 hours after admission 19 COPD/astma exacerbation requiring corticosteroid therapy 9 recent corticosteroid use (>30 mg daily) 6 need for corticosteroids judged by attending physician 5 Using macrolides prior to admission 3 no follow up possible 2 active cancer

Table E2

Pre-admission antibiotics	Prednisolone (n=104)	Placebo (n=109)
none	78 (75.0%)	84 (77.1%)
Amoxicillin	7 (6.7%)	7 (6.4%)
Amocillin/clavulanic acid	16 (15.4%)	11 (10.1%)
Doxycyclin	1 (1.0%)	4 (3.7%)
Co-trimoxazole	2 (2.0%)	2 (1.8%)
Flucloxacillin	0	1 (0.9%)

Table E3. Antibiotic use prior to hospital admission

Pre-admission antibiotics	Prednisolone (n=104)	Placebo (n=109)
none	78 (75.0%)	84 (77.1%)
Amoxicillin	7 (6.7%)	7 (6.4%)
Amocillin/clavulanic acid	16 (15.4%)	11 (10.1%)
Doxycyclin	1 (1.0%)	4 (3.7%)
Co-trimoxazole	2 (2.0%)	2 (1.8%)
Flucloxacillin	0	1 (0.9%)

Data are presented as mean (percentage)