Efficacy of Corticosteroids in Community-acquired Pneumonia

A Randomized Double-Blinded Clinical Trial

Dominic Snijders[1], Johannes M. A. Daniels[2], Casper S. de Graaff[1], Tjip S. van der Werf[3], and Wim G. Boersma[1]

[1]Department of Pulmonary Diseases, Medical Center Alkmaar, Alkmaar, The Netherlands; [2]Department of Pulmonology, VU University Medical Center, Amsterdam, The Netherlands; and [3]Departments of Internal Medicine and Pulmonary Diseases and Tuberculosis, University Medical Center Groningen, University of Groningen, the Netherlands

***Rationale*: Some studies have shown a beneficial effect of corticosteroids in patients with community-acquired pneumonia (CAP), possibly by diminishing local and systemic antiinflammatory host response.**

***Objectives*: To assess the efficacy of adjunctive prednisolone treatment in patients hospitalized with CAP.**

***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, along with 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. Disease severity was scored using CURB-65 (a severity index for community-acquired pneumonia evaluating Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older) and Pneumonia Severity Index.**

***Measurements and Main Results*: We enrolled 213 patients. Fifty-four (25.4%) patients had a CURB-65 score greater than 2, and 93 (43.7%) patients were in Pneumonia Severity Index class IV-V. Clinical cure at Days 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 C-reactive protein levels compared with placebo. Subanalysis of patients with severe pneumonia did not show differences in clinical outcome. Late failure (>72 h after admittance) was more common in the prednisolone group (20 patients, 19.2%) than in the placebo group (10 patients, 6.4%; $P = 0.04$). Adverse events were few and not different between the two groups.**

***Conclusions*: 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.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00170196).

Keywords: community-acquired pneumonia; corticosteroids; infection

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Corticosteroids are used in patients with sepsis or septic shock, of which a large part is due to pneumonia. The use of corticosteroids along with antibiotics in patients with community-acquired pneumonia (CAP) may lead to a diminished local and systemic antiinflammatory response.

What This Study Adds to the Field

Prednisolone as an adjunctive treatment along with antibiotics does not improve outcome in hospitalized patients with CAP and may lead to more late failure in patients with nonsevere CAP.

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide (1). Despite the developments in antibiotic therapy, no substantial progress has been made in the last decades (2). Additional therapeutic interventions along with 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, whereas 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 Corticosteroid Therapy of Septic Shock 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 Pa_{O_2}/FI_{O_2} and also a survival advantage in patients with severe CAP admitted to the intensive care unit (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 along with 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-day mortality, defervescence, and serum C-reactive protein levels (CRP).

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Correspondence and requests for reprints should be addressed to Dominic Snijders, M.D., Department of Pulmonary Diseases, Medical Centre Alkmaar, Wilhelminalaan 15, 1812 JD Alkmaar, The Netherlands. E-mail: d.snijders@mca.nl

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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 dyspnea. (*3*) New consolidations on chest radiograph. (*4*) Age 18 years or older.

Patients were excluded from the study if one of the following criteria applied: Presence of severe immunosuppression (HIV infection, use of immunosuppressants), malignancy, pregnancy or breast-feeding, use of macrolides for more than 24 hours, use of prednisone 15 mg or more 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 [severity index for community-acquired pneumonia evaluating Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older] score > 2 or PSI class IV and V) 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 (intravenous or oral). When patients were switched from intravenous to oral antibiotics the study drug was also switched. Randomization was based on a one-on-one allocation by means of prenumbered containers containing seven vials for intravenous administrations and seven 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 antibiotic treatment was allowed but the use of macrolides was discouraged because of their 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 intravenous 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, hematology, and CRP (Beckman Coulter Inc., Fullerton, CA). 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 Day 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 extrapulmonary infection, or the deterioration of chest radiography after randomization, or death due to pneumonia,

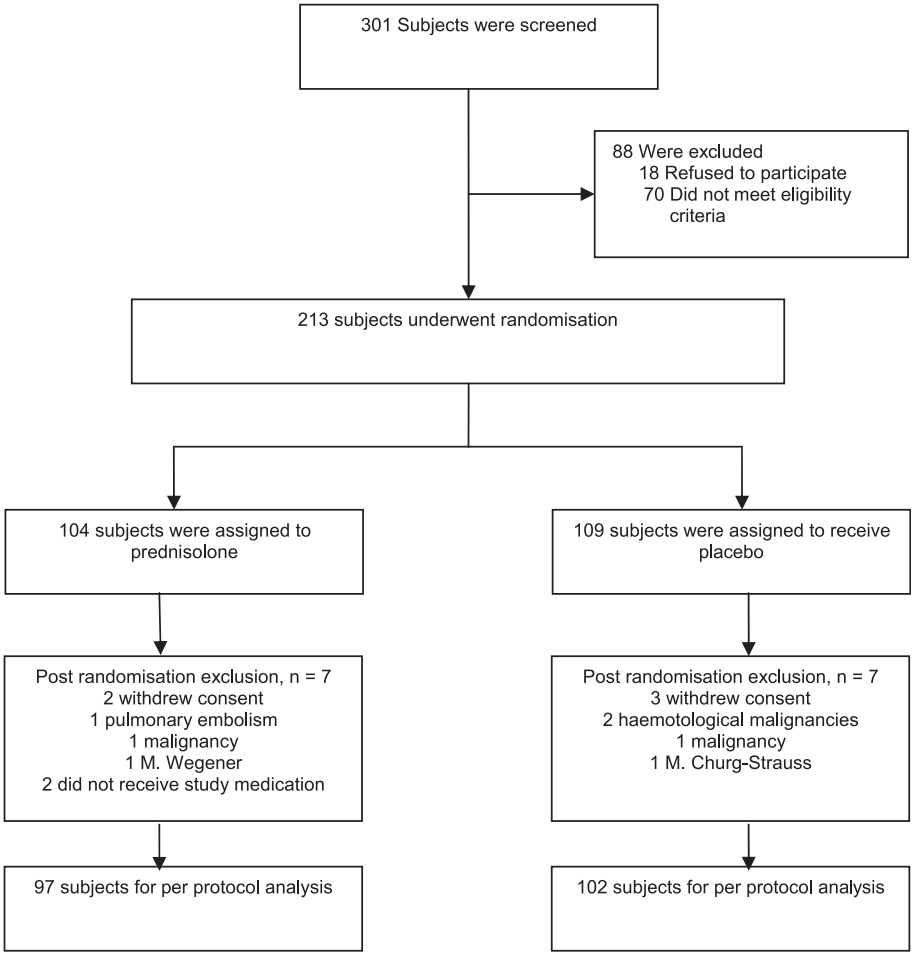

Figure 1. Study flow chart.

TABLE 1. DEMOGRAPHIC FEATURES OF THE INTENTION-TO-TREAT GROUP OF HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA (N = 213)

	Prednisolone Group (*n = 104*)	Placebo Group (*n = 109*)	*P* Value
Age, yr	63.0 ± 17.9	64.0 ± 18.7	0.67
Male sex	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, mm Hg	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, breaths/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, $\times 10^9$/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

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CURB-65 = severity index for community-acquired pneumonia evaluating Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older; ICU = intensive care unit; WBC = white blood cell count.

Data are presented as n (%) or mean ± SD.

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 after an initially beneficial response to treatment.

Time to clinical stability was assessed by using the criteria defined by Halm and colleagues (14). In short, patients were clinically stable if all four of the following criteria were met: improvement of cough and shortness of breath, temperature less than 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 less than 37.5°C.

Microbiological Investigations

At admission, a sputum specimen was ordered for Gram stain, semiquantitative 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 *S. pneumoniae* and *L. pneumophila* serogroup 1 (enzyme immunoassay, Binax-NOW; Binax, Portland, ME). Pleural fluid if present was examined by Gram stain, culture, and *S. pneumoniae* antigen test.

Blood samples for serology (Serion ELISA classic; Virion GmbH, Würzburg, Germany) were obtained on Day 1 and Day 14 of the study for detection of antibodies to *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *L. 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 α 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 exact test for categorical variables

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-d Mortality	6/104 (5.8)	6/109 (5.5)	0.93	1.05 (0.33–3.37)
LOS, d	10.0 ± 12.0	10.6 ± 12.8	0.16	−0.56 (−4.00 to 2.8)
TTCS, d	4.9 ± 6.8	4.9 ± 5.2	0.97	0.03 (−1.6 to 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-d Mortality	6/97 (6.2)	6/102 (5.9)	0.93	1.06 (0.33–3.39)
LOS, d	10.0 ± 12.1	10.4 ± 13.1	0.83	−0.40 (−4.01 to 3.22)
TTCS, d	5.0 ± 7.0	4.9 ± 5.3	0.90	0.12 (−1.68 to 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)

Definition of abbreviations: CI = confidence interval; LOS = length of stay; TTCS = time to clinical stability.
All data are presented as n (%) or mean ± SD.

and a two-sample *t* test or Mann–Whitney test for continuous variables. The Kaplan-Meier method was used to analyze 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 Days 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%] vs. 26 [12.2%] patients; $P = 0.61$; PSI IV–V: 48 [46.2%] vs. 45 [41.3%] patients; $P = 0.47$). Reasons for exclusion are listed in Table E1 in the online supplement.

Antibiotic Treatment

Antimicrobial treatment was similar in both study arms (Table 2). Twenty-six (25.0%) patients in the prednisolone group and 25 (22.0%) patients in the placebo group were using antibiotics before admission (Table E2).

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 groups (80.8% vs. 85.3%; $P = 0.38$). Kaplan-Meier plots of LOS and TTCS are shown in Figures 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 1 patient with asthma), withdrawal of informed consent in 5 patients, and postrandomization exclusion in 8 patients. There were no differences between the prednisolone group and the placebo group in the need for additional corticosteroids (six [5.8%] vs. 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 Day 2 ± 1 day in the prednisolone group and Day 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 with patients in the placebo group (41.73 ± 64.98 vs. 22.05 ± 53.32 mg/L; $P < 0.01$).

In patients with nonsevere CAP late failures occurred more often in the prednisolone group than in the placebo group (CURB-65 0–2; 15/76 vs. 5/87 patients; $P < 0.01$ and PSI classes I–III; 10/56 vs. 4/64 patients; $P = 0.05$).

In the prednisolone group, five (4.8%) patients with late failure needed an additional course of antibiotics, seven (6.7%) patients needed another or a prolonged course of prednisolone, and six (5.8%) patients developed a pleural effusion or empyema necessitating additional therapy. In the placebo group, two (1.8%) patients needed additional antibiotics, three (2.8%) patients needed a course of prednisolone, and one patient developed a pleural effusion requiring additional therapy.

Subanalysis of primary and secondary outcome parameters in patients with severe CAP (CURB-65 > 2 or PSI class 4–5)

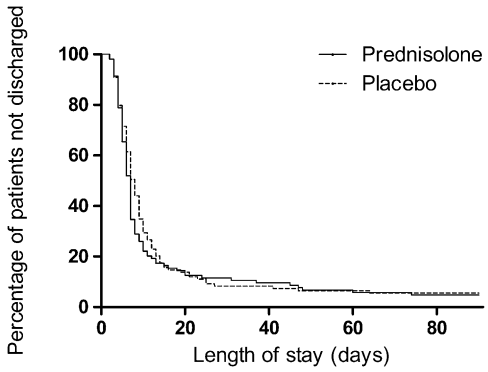

Figure 2. Kaplan-Meier curves showing the effect of the intervention on length of stay in the intention-to-treat population. *Solid line* = prednisolone; *dashed line* = placebo. Log rank, 0.84; hazard ratio, 1.15; 95% confidence interval, 0.81–1.55; $P = 0.36$.

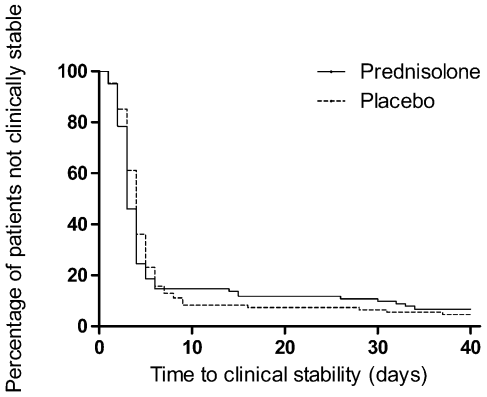

Figure 3. Kaplan-Meier curves showing the effect of the intervention on time to clinical stability in the intention-to-treat population. *Solid line* = prednisolone; *dashed line* = placebo. Log rank, 0.60; hazard ratio, 1.14; 95% confidence interval, 0.82–1.59; $P = 0.44$.

are shown in Table 4. Subanalysis of mechanically ventilated patients showed no differences in the primary and secondary outcome parameters (Table E3).

Cause

An etiological diagnosis for CAP was made in 118 (55.4%) patients; *S. pneumoniae* (78 [36.6%]) was the most frequently found causative microorganism. 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%] vs. 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] vs. 4 [IQR, 2] d; $P = 0.01$), a shorter LOS (5.5 [IQR, 3] vs. 7 [IQR 7] d; $P = 0.03$), and faster defervescence (2 [IQR, 1] vs. 3 [IQR, 3] d; $P < 0.01$). 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 five (2.3%) patients in the prednisolone group and two (0.9%) patients in the placebo group ($P = 0.27$). Confusion during admission was noted in four (1.9%) patients in the prednisolone group and in three (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 10 days after 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

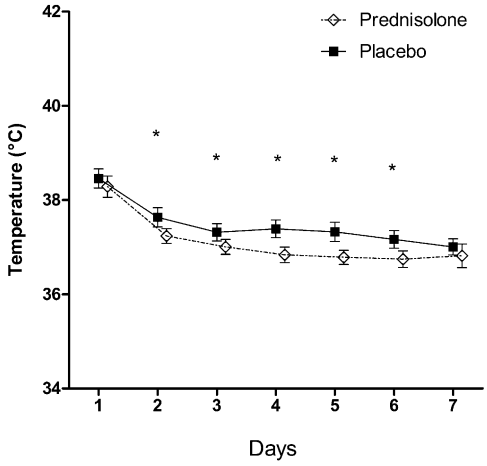

Figure 4. Defervescence in patients with community-acquired pneumonia treated with prednisolone or placebo. *Diamonds* = pednisolone; *squares* = placebo. Data are presented as mean ± SD. * $P < 0.01$.

patients hospitalized with CAP; clinical cure was equal in both groups at Day 7. A trend toward 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

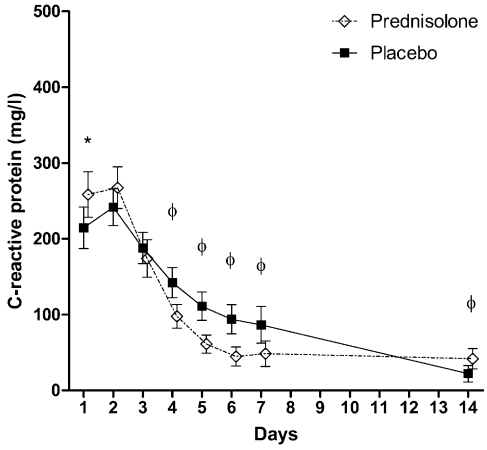

Figure 5. Serum C-reactive protein levels during treatment and at Day 14 for patients in both study groups. *Diamonds* = pednisolone; *squares* = placebo. Data are presented as mean ± SD. * $P = 0.03$; $^{\phi}$ $P < 0.01$.

TABLE 4. SUBANALYSIS OF CLINICAL OUTCOME OF SEVERE PNEUMONIA AS DEFINED BY CURB-65 SCORE GREATER THAN 2 OR PNEUMONIA SEVERITY INDEX CLASS LESS THAN III 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-d Mortality	4/48 (14.3)	3/45 (11.5)	0.76	1.28 (0.26–6.35)
LOS, d	19.4 ± 20.2	20.4 ± 22.7	0.87	−1.00 (−13.24 to 11.24)
TTCS, d	9.9 ± 11.2	8.7 ± 9.8	0.72	1.13 (−5.18 to 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 classes 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-d Mortality	5/48 (10.4)	5/45 (11.1)	0.91	0.93 (0.25–3.46)
LOS, d	15.0 ± 16.4	16.4 ± 18.4	0.71	−1.38 (−8.85 to 6.09)
TTCS, d	7.7 ± 9.8	6.8 ± 7.6	0.68	1.96 (−3.07 to 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)

Definition of abbreviations: CI = confidence interval; CURB-65 = severity index for community-acquired pneumonia evaluating Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older; LOS = length of stay; TTCS = time to clinical stability.

All data are presented as n (%) or mean ± SD.

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 Corticosteroid Therapy of Septic Shock 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 nonresponders to a corticotrophin test. In our study, subanalysis 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 and colleagues (8, 19). Also, the absolute numbers of patients who needed mechanical ventilation was low. Gotoh and colleagues (20) examined adrenal insufficiency in 64 patients hospitalized with CAP and found a low incidence of adrenal insufficiency in this population. Only 14% fulfilled the criteria for adrenal insufficiency. Adrenal insufficiency is probably not clinically relevant in patients with nonsevere 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 Mikami and colleagues (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 had a low number of included patients and the open-label design. The antiinflammatory 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 clinically 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, after an initially faster decline in the first week. This rebound phenomenon is also observed in the study by Garcia-Vidal and colleagues (9). Nonsurvivors on corticosteroid therapy died later than nonsurvivors without corticosteroids (13.8 vs. 7.1 d, respectively). 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 nonsurvivors 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 metaanalysis found no evidence of increased risk for nosocomial infections in corticosteroid-treated patients (3). In our study, the inclusion of patients with nonsevere 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

TABLE 5. CAUSE OF COMMUNITY-ACQUIRED PNEUMONIA IN 231 PATIENTS

	Prednisolone Group (*n = 104*)	Placebo Group (*n = 109*)
Streptococcus pneumoniae	42 (40.4)	36 (33.0)
Mycoplasma pneumoniae	7 (6.7)*	7 (6.4)
Legionella 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*.

† One mixed infection influenza A/*Haemophilus influenzae*, two mixed infection influenza A/*S. pneumoniae*.

‡ One mixed infection *M. pneumoniae*/*S. pneumoniae*.

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. Second, 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 underrepresentation 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%, whereas 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 nonsevere pneumonia. But even in this case, the number needed to treat to detect a favorable 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 nonsevere 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 believe this limits our findings.

The Dutch guidelines concerning antibiotic therapy in patients with CAP differ from the Infectious Diseases Society of America/American Thoracic Society 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 support the antibiotics used in this study conducted in the Netherlands (28, 29)

As the 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 pharmacodynamic 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 1 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 nonsevere CAP and lack of benefit, prednisolone should not be recommended as routine adjunct treatment in CAP.

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