Corticosteroids and pneumonia: time to change practice

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Pneumonia is characterised by lung inflammation, with fluid filling the alveoli and preventing adequate oxygenation of the body, and can be acquired in the community or in hospital. In 2013, about one million children died from pneumonia, which was the leading cause of death in children aged 5 years or younger.[1] Annually, 15 adults per 1000 visit a doctor for symptoms of community-acquired pneumonia.[2] In 2013, lower respiratory tract infections caused 2·7 million deaths.[1] Although the epidemiological burden of community-acquired pneumonia is highest in patients aged 65 years or older, the disease incurs substantial morbidity and health-care costs in working-age adults.[3]

Management of this disorder relies mainly on empirical antibiotic treatment, and so far no adjunct therapy is recommended.[4] In *The Lancet*, Claudine Angela Blum and colleagues[5] report that 7-day treatment with 50 mg oral prednisone daily hastened recovery and hospital discharge in adults with community-acquired pneumonia of any severity.[5] Compared with controls (who received placebo), clinical stability was achieved 1·4 days earlier in the corticosteroid-treated patients (3·0 days in the prednisone group *vs* 4·4 days in the control group; hazard ratio [HR] 1·33, 95% CI 1·15–1·50), who subsequently spent 1 day less in hospital. Treatment with prednisone was well tolerated except for transient mild-to-moderate hyperglycaemia (76 [19%] *vs* 43 [11%]; OR 1·96, 95% CI 1·31–2·93). This trial was appropriately designed to minimise selection bias and possible confounding, and powered to show the efficacy of corticosteroids convincingly.

The favourable benefit-to-risk ratio noted with corticosteroids in this trial is in line with findings from trials done in Egypt,[6] Italy,[7] Japan,[8] the Netherlands,[9] and Spain.[10] Only one trial[11] did not show benefit from corticosteroids. Data from five of these six trials accounting for 1379 adults with community-acquired pneumonia showed that adjunct treatment with corticosteroids reduced length of hospital stay (mean difference –1·10 days, 95% CI –1·86 to –0·34; figure), time on intravenous antibiotics (–0·69 days, –1·21 to –0·17, three trials, 1120 patients; appendix), and time to clinical stability (–1·41 days, –2·18 to –0·64; three trials, 1029 patients). In these trials, observed mortality of control patients in the short term ranged from 0% to 7% in patients not in the intensive care unit (ICU),[5,6,8,11] and from 15% to 30% in those in ICU.[7,9,10]

Corticosteroids might provide survival benefit for adults with community-acquired pneumonia requiring admission to the ICU (appendix). I believe that corticosteroids improve outcomes in patients with pneumonia mainly by alleviating lung and systemic inflammation without causing immune suppression. Indeed, they induce a rapid and sustained decrease in concentrations of circulating inflammatory markers such as C-reactive protein[5–11] and interleukin 6.[8] Subsequently, inflammation-related symptoms such as fever, breathlessness, tachycardia, and hypoxia resolve faster in patients treated with systemic corticosteroids than in those treated with placebo.[5–11] Owing to unaltered concentrations of anti-inflammatory molecules such as interleukin 10,[5,10] adjunct treatment with corticosteroids do not increase the risk of secondary infections.[5–11]

See Online for appendix

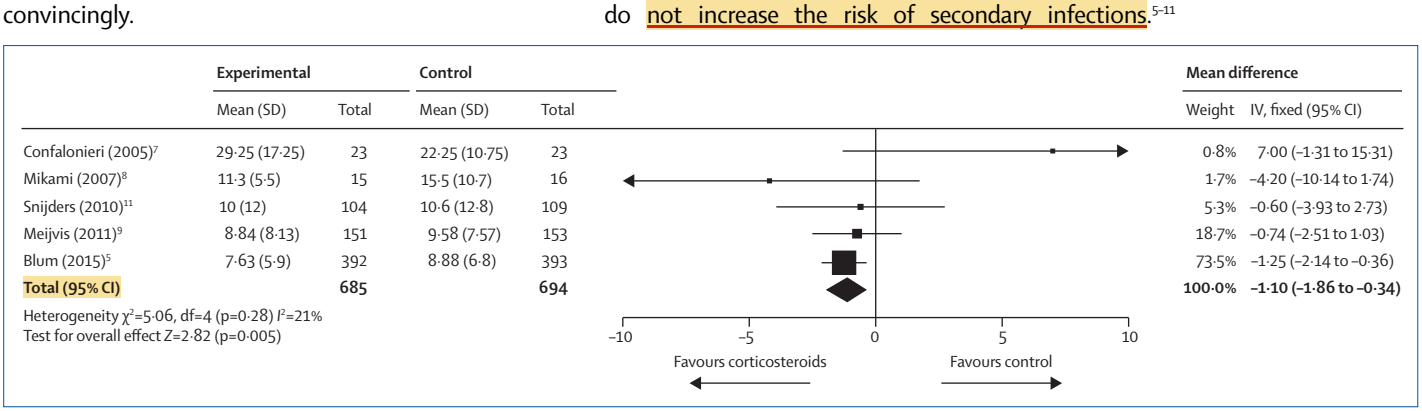

Figure: **Mean difference of length of hospital stay in adults admitted to hospital with community-acquired pneumonia who received corticosteroid treatment or placebo**
I calculated the pooled mean difference with a fixed-effects model and noted no heterogeneity for the analysis including all trials. In the forest plot, for each individual trial, the mean difference is represented as a black square in the centre of the black line corresponding to the 95% CI; the size of the black square is proportional to trial's weight.

In my experience, the transient increase in blood glucose concentrations following corticosteroid administration[5,8] is unlikely to harm patients.

As the Northern hemisphere is entering the period of seasonal influenza, with recrudescence of lower respiratory tract infections, Blum and colleagues' trial[5] provides valuable evidence to recommend adjunct 7-day treatment with 50 mg oral prednisone for the management of adults admitted to hospital with community-acquired pneumonia. In my opinion, the accelerated recovery of wellbeing and reduction of hospital stay is of major added value. In European countries, the median estimated cost of median length of stay ranges from €1200 to €6900, with most of the expenses being related to hospital stay and staff.[12] Therefore, the corticosteroid-associated reduction in length of hospital stay should translate into substantial cost savings. Likewise, reduction in the use of antibiotics is potentially of major added value for the community. As UK Prime Minister David Cameron has said, the world could soon be "cast back into the dark ages of medicine unless action is taken to tackle the growing threat of resistance to antibiotics".[13]

Unanswered issues remain, on which researchers should focus their attention. First, evidence for a benefit from corticosteroids in outpatients with community-acquired pneumonia is still missing, although exploratory analyses done by Blum and colleagues did not suggest an interaction between disease severity and responses to corticosteroids.[5] Second, the survival benefit of corticosteroids in patients with community-acquired pneumonia in the ICU still needs large confirmatory trials. Finally, researchers should also investigate any possible long-term benefit from corticosteroids owing to the growing evidence of long-term sequelae following severe infections.[14]

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I declare no competing interests.

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Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background **Clinical trials yielded conflicting data about the benefit of adding systemic corticosteroids for treatment of community-acquired pneumonia. We assessed whether short-term corticosteroid treatment reduces time to clinical stability in patients admitted to hospital for community-acquired pneumonia.**

Methods **In this double-blind, multicentre, randomised, placebo-controlled trial, we recruited patients aged 18 years or older with community-acquired pneumonia from seven tertiary care hospitals in Switzerland within 24 h of presentation. Patients were randomly assigned (1:1 ratio) to receive either prednisone 50 mg daily for 7 days or placebo. The computer-generated randomisation was done with variable block sizes of four to six and stratified by study centre. The primary endpoint was time to clinical stability defined as time (days) until stable vital signs for at least 24 h, and analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00973154.**

Findings **From Dec 1, 2009, to May 21, 2014, of 2911 patients assessed for eligibility, 785 patients were randomly assigned to either the prednisone group (n=392) or the placebo group (n=393). Median time to clinical stability was shorter in the prednisone group (3·0 days, IQR 2·5–3·4) than in the placebo group (4·4 days, 4·0–5·0; hazard ratio [HR] 1·33, 95% CI 1·15–1·50, p<0·0001). Pneumonia-associated complications until day 30 did not differ between groups (11 [3%] in the prednisone group and 22 [6%] in the placebo group; odds ratio [OR] 0·49 [95% CI 0·23–1·02]; p=0·056). The prednisone group had a higher incidence of in-hospital hyperglycaemia needing insulin treatment (76 [19%] *vs* 43 [11%]; OR 1·96, 95% CI 1·31–2·93, p=0·0010). Other adverse events compatible with corticosteroid use were rare and similar in both groups.**

Interpretation **Prednisone treatment for 7 days in patients with community-acquired pneumonia admitted to hospital shortens time to clinical stability without an increase in complications. This finding is relevant from a patient perspective and an important determinant of hospital costs and efficiency.**

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Introduction

Respiratory tract infections and pneumonia in particular are the third-leading cause of death worldwide.[1] Although outcome of community-acquired pneumonia improved with the availability of antibiotics, this disorder still carries a high risk for long-term morbidity and mortality.[2] Adjunct therapeutic interventions could improve outcome of patients with this type of pneumonia.

In community-acquired pneumonia, an excessive release of circulating inflammatory cytokines can be harmful and cause pulmonary dysfunction. Systemic corticosteroids have anti-inflammatory effects, attenuating the systemic inflammatory process in the disorder.[3] Therefore, adjunct treatment with corticosteroids has been discussed since the 1950s, when favourable effects of corticosteroids were noted in pneumococcal pneumonia.[4] More recently, a significant reduction of in-hospital mortality in patients with severe community-acquired pneumonia was noted in a small randomised trial[5] (n=46) testing a 7-day continuous infusion of hydrocortisone versus placebo. A retrospective single-centre study[6] including 308 patients suggested that the use of corticosteroids was associated with decreased mortality. Two recent randomised placebo-controlled trials[7,8] including 200–300 patients revealed controversial results. Whereas the first trial[7] did not find any benefit of adjunct prednisolone, but an increased recurrence rate, the second trial[8] in which patients received intravenous dexamethasone over 4 days reported a significant reduction in length of hospital stay by 1 day. Two systematic reviews[9,10] and three meta-analyses[11–13] concluded that adjunct corticosteroids in community-acquired pneumonia might be beneficial, but a large, adequately powered randomised trial is warranted.

Therefore, we investigated the effects of short-term prednisone versus placebo in patients admitted to hospital for community-acquired pneumonia with the primary endpoint of time to clinical stability.

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Methods

Study design and participants

This is an investigator-initiated, multicentre, double-blind, randomised, placebo-controlled trial. Details of the trial design have previously been published.[14] In brief, consecutive patients presenting with community-acquired pneumonia were screened and enrolled at emergency departments or medical wards in seven tertiary care hospitals in Switzerland from Dec 1, 2009, to May 21, 2014, within 24 h of presentation. Inclusion criteria were age 18 years or older and hospital admission with community-acquired pneumonia defined by a new infiltrate on chest radiograph and the presence of at least one of the following acute respiratory signs and symptoms: cough, sputum production, dyspnoea, core body temperature of 38·0°C or higher, auscultatory findings of abnormal breathing sounds or rales, leucocyte count higher than 10 000 cells per µL or less than 4000 cells per µL.[15] Exclusion criteria were permanent inability for informed consent, active intravenous drug use, acute burn injury, gastrointestinal bleeding within the past 3 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 350 cells per µL, immunosuppressive therapy after solid organ transplantation, neutropenia below 500 cells per µL or neutrophils of 500–1000 cells per µL during ongoing chemotherapy with an expected decrease to values below 500 cells per µL, cystic fibrosis, or active tuberculosis. The conduct of the trial adhered to the declaration of Helsinki and Good Clinical Practice Guidelines, and ethical committees of all participating hospitals approved the study before patient recruitment. All patients provided written informed consent.

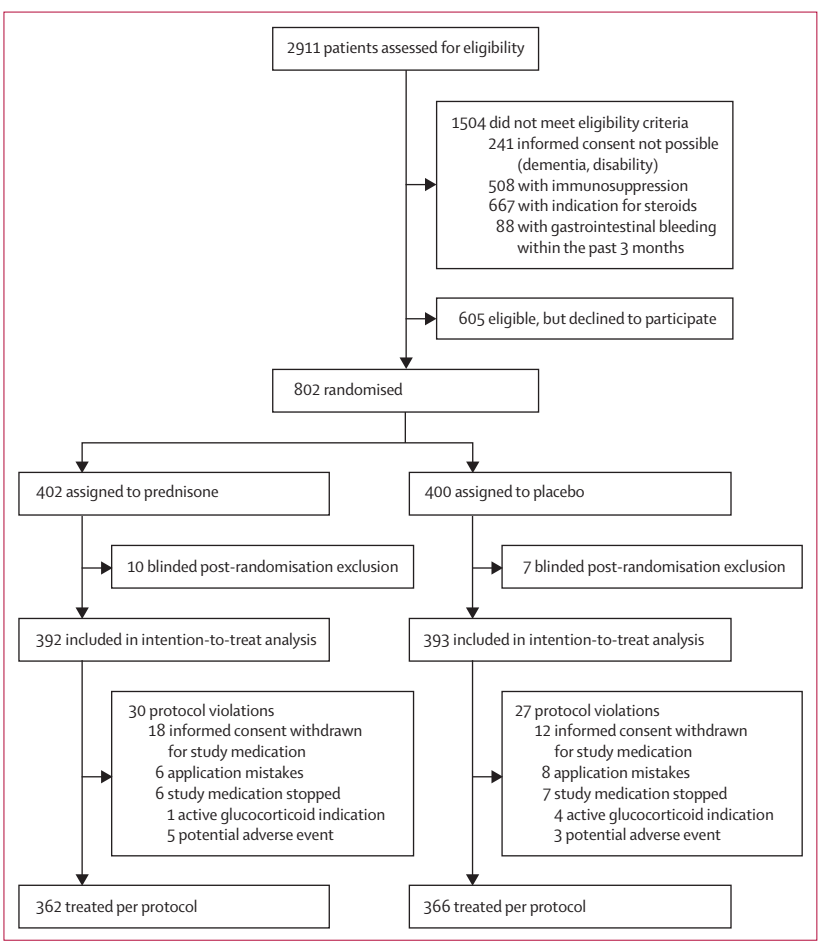

Figure 1: **Trial profile**
No patient was lost to follow-up before reaching the primary endpoint. One patient in the prednisone group and three patients in the placebo group were lost to follow-up at 30 days.

Randomisation and masking

Eligible patients were randomly assigned (1:1 ratio) to receive either 50 mg of prednisone or placebo daily for 7 days. Randomisation was done with variable block sizes of four to six and patients were stratified at the time of study entry by study centre. Allocation was concealed with a prespecified computer-generated randomisation list, which was centrally kept at the pharmacy of the main study centre.

Patients were randomly assigned to receive a prepared set of study medication that contained seven tablets of 50 mg prednisone or placebo. The placebo drug was purchased from a local prednisone manufacturer (Galepharm AG, Küsnacht, Switzerland), which produces both prednisone and its corresponding placebo. The drugs were prepared before the initiation of the study and packed into identical containers by the Pharmacology Department, University Hospital, Basel, according to the randomisation list. Patients, treating physicians, investigators, and data assessors were masked to treatment allocation.

Procedures

After informed consent was obtained, baseline blood samples were drawn and nasal swabs for virus multiplex PCR were done. All other microbiological assessments were at the discretion of the treating physicians. Patients started antibiotic therapy as soon as community-acquired pneumonia was confirmed. Treating physicians chose the empirical regimen according to the ERS/ESCMID guidelines adapted for Switzerland.[16,17] Most patients started this regimen either with amoxicillin plus clavulanic acid or ceftriaxone alone. In patients with clinical suspicion for legionellosis or in those requiring treatment in the intensive care unit (ICU), the beta-lactam was combined with clarithromycin. Treatment was streamlined and optimised according to the susceptibility pattern as soon as a specific pathogen was known. Thereafter, patients started receiving study medication, and we monitored timing in relation to start of antibiotics. Study nurses assessed patients for clinical stability every 12 h during hospital stay. All patients were

treated according to published community-acquired pneumonia guidelines.[18] Stewardship of antibiotic treatment duration by procalcitonin was encouraged by the study protocol according to Schuetz and colleagues.[19] 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).[20] Routine laboratory tests of inflammatory markers (procalcitonin, C-reactive protein [CRP], white blood cell count) were done in both groups on days 1, 3, 5, 7, and before discharge and included four glucose measurements per day.

Structured follow-up telephone interviews for secondary outcomes after discharge were done on day 30 and included assessment of adverse events such as infections, recurrent pneumonia, re-admission to hospital, new onset diabetes or insulin dependence, and new onset hypertension.

Outcomes

The primary endpoint was time to clinical stability defined as time (days) until stable vital signs for 24 h or longer. Stable vital signs were 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%), which were based on current community-acquired pneumonia treatment recommendations.[15] Instability was defined if at least one of these criteria were not met.

Secondary endpoints were time to effective discharge from hospital, recurrence of pneumonia, re-admission to hospital, ICU admission, all-cause mortality, duration of total and intravenous antibiotic treatment, disease activity scores specific to community-acquired pneumonia,[21] incidence of complications due to community-acquired pneumonia (ie, acute respiratory distress syndrome, empyema, persistence of pneumonia), side-effects of corticosteroids (ie, rate of hyperglycaemia, hypertension, delirium, nosocomial infections, and weight gain), and time to earliest possible hospital discharge.

For patients admitted to ICU we recorded length of ICU stay, time to transfer to ICU, time to discharge from ICU, duration of vasopressor treatment, and duration of mechanical ventilation.

Statistical analysis

The statistical analysis was prespecified, and investigators who analysed the data were masked to treatment allocation.[14] The primary hypothesis of this trial was that corticosteroids will reduce time to clinical stability in patients with community-acquired pneumonia without relevant adverse effects. On the basis of previous trials,[19,22] we assumed a mortality rate of 10% in the placebo group and 7·5% in the corticosteroid group over 14 days of follow-up with a proportion of 75% survivors being clinically stable after 7 days in the corticosteroid group. Estimating a decrease in the risk of non-stability after 1 week in survivors by 25% through adjunct corticosteroids, we calculated that we needed a sample size of 800 patients followed up for at least 14 days to achieve a statistical power of 85%.

	Prednisone (n=392)	Placebo (n=393)
General characteristics		
Age, years	74 (61–83)	73 (61–82)
Male sex	241 (61%)	246 (63%)
Clinical variables		
Days with symptoms	4·0 (2·0–7·0)	4·0 (2·0–7·0)
Temperature (°C)	37·6 (37·0–38·2)	37·6 (37·0–38·2)
Systolic blood pressure (mm Hg)	124 (110–140)	123 (110–140)
Heart rate (beats per min)	84 (74–95)	82 (72–96)
Respiratory rate (breaths per min)	20 (18–24)	20 (18–24)
SaO_2 (%)	95 (92–96)	94 (92–97)
Bacteraemia	39 (10%)	48 (12%)
Confusion	22 (6%)	29 (7%)
CAP score (points)*	43 (30–60)	46 (29–63)
Laboratory values		
Procalcitonin (ng/mL)	0·52 (0·18–2·51)	0·50 (0·17–2·63)
C-reactive protein (mg/L)	159 (80·3–245)	164 (79·1–250)
White-blood-cell count (cells per µL)	12 200 (8900–15 800)	11 900 (8700–15 600)
Glucose (fasting morning, mmol/L)	6·3 (5·4–7·8)	6·5 (5·8–7·7)
PSI score†		
PSI class I	47 (12%)	45 (11%)
PSI class II	72 (18%)	69 (18%)
PSI class III	71 (18%)	95 (24%)
PSI class IV	148 (38%)	132 (34%)
PSI class V	54 (14%)	52 (13%)
Total PSI score (points)	93 (63–115)	86 (65–110)
Comorbidities		
Diabetes mellitus (any type)	77 (20%)	78 (20%)
Insulin treatment	44 (11%)	35 (9%)
Chronic obstructive pulmonary disease	73 (19%)	60 (15%)
Heart failure	80 (20%)	62 (16%)
Cerebrovascular disease	38 (10%)	31 (8%)
Renal insufficiency	125 (32%)	126 (32%)
Neoplastic disease	29 (7%)	25 (6%)
Liver disease	17 (4%)	12 (3%)
Co-infections‡	45 (11%)	46 (12%)
Antibiotic pretreatment	84 (21%)	95 (24%)

Data are median (IQR) or number (%), unless otherwise stated. SaO_2=saturation of oxygen. PSI=pneumonia severity index. *The CAP score is a disease-specific activity score for community-acquired pneumonia; it ranges from 0 to 100, 0 marking the worst, 100 the best score.[21] †The PSI is a clinical prediction rule to calculate the probability of morbidity and mortality in patients with community-acquired pneumonia;[20] PSI risk class I corresponds to age ≤50 years, and no risk factors (≤50 points), risk class II to <70 points, risk class III to 71–90 points, risk class IV to 91–130 points, and risk class V to >130 points. ‡Nine skin infections, 43 urinary tract infections, 28 upper respiratory tract infections, ten gastrointestinal tract infections, and one joint infection.

Table 1: **Baseline characteristics of enrolled patients**

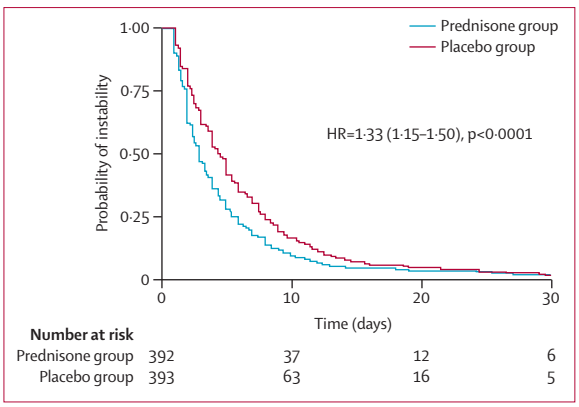

Figure 2: **Kaplan-Meier-curve of time to clinical stability**

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			HR, OR, or difference (95% CI)	p value
Primary endpoint				
Intention-to-treat: time to clinical stability, days	3·0 (2·5–3·4)	4·4 (4·0–5·0)	HR 1·33 (1·15 to 1·50)	<0·0001
Per-protocol: time to clinical stability, days	3·0 (2·5–3·2)	4·4 (4·0–5·0)	HR 1·35 (1·16 to 1·56)	<0·0001
Secondary endpoints				
Time to effective hospital discharge, days	6·0 (6·0–7·0)	7·0 (7·0–8·0)	HR 1·19 (1·04 to 1·38)	0·012
Recurrent pneumonia	23 (6%)	18 (5%)	OR 1·30 (0·69 to 2·44)	0·42
Re-admission to hospital	32 (9%)	28 (8%)	OR 1·14 (0·67 to 1·93)	0·64
ICU admission	16 (4%)	22 (6%)	OR 0·72 (0·37 to 1·39)	0·32
Time to ICU admission, days	1 (1–1)	1 (1–1)	HR 0·73 (0·38 to 1·38)	0·33
Time in ICU, days	3 (2–4)	3 (1–12)	Difference −0·2 days (−8·7 to 8·2)	0·96
Death from any cause	16 (4%)	13 (3%)	OR 1·24 (0·59 to 2·62)	0·57
Time to death, days	8·0 (3·0–22·0)	9·0 (2·0–12·0)	HR 1·23 (0·59 to 2·55)	0·59
Total duration of antibiotic treatment, days	9·0 (7·0–11·0)	9·0 (7·0–12·0)	Difference −0·47 days (−1·21 to 0·27 days)	0·22
Intravenous antibiotic treatment, days	4·0 (3·0–6·0)	5·0 (3·0–7·0)	Difference −0·89 days (−1·57 to −0·20) days)	0·011
CAP score* at day 5, points	59 (41–78)	58 (40–74)	Difference 1·00 (−5·23 to 7·23)	0·75
CAP score* at day 30, points	83 (67–88)	84 (72–89)	Difference −1·00 (−4·38 to 2·38)	0·56

Data are median (IQR) or number (%) unless otherwise stated. HR=hazard ratio. OR=odds ratio. ICU=intensive care unit. *The CAP score is a disease-specific activity score for community-acquired pneumonia. It ranges from 0 to 100, 0 marking the worst, 100 the best score.[21]

Table 2: **Overview of primary and secondary endpoints**

The primary analysis followed the intention-to-treat principle, which means that patients were analysed in the groups to which they were randomly assigned, independent of whether they took the allocated treatment.[14] The per-protocol population focused on patients fully complying with the trial protocol. For the primary endpoint, we calculated an unadjusted hazard ratio (HR) and 95% CI using Cox proportional hazards regression based on a binary outcome of achieving or not achieving clinical stability. 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. As a sensitivity analysis, the primary analysis was repeated on the per-protocol population. As a further sensitivity analysis, a multivariable Cox proportional hazards model was fitted with treatment group and prespecified potential confounders patient age and PSI score as independent variables.[14] We did prespecified subgroup analyses (patient age, initial CRP concentration, history of chronic obstructive pulmonary disease [COPD], PSI class, blood culture positivity) by including appropriate interaction terms in the multivariable Cox proportional hazards model.[14]

For all secondary endpoints, we calculated unadjusted and adjusted (for patient age and PSI score) estimates of the effect size and corresponding 95% CIs using linear, logistic, or Cox proportional hazards regression (as appropriate). We analysed community-acquired pneumonia scores using non-parametric linear models (quantile regression) due to substantially skewed distributions.[23] For all time-to-event analyses of secondary endpoints, patients lost to follow-up were censored at the time of lost contact; for all other analyses of secondary outcomes we used complete case analyses.

All reported CIs are two-sided 95% intervals, and tests were done at the two-sided 5% significance level. We used STATA 12·1 (Stata Corp, College Station, Texas) for all analyses. This trial is registered with ClinicalTrials.gov, number NCT00973154.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 802 eligible patients in the trial and randomly assigned them to receive either prednisone or placebo (figure 1). After blinded post-randomisation exclusion of 17 patients retrospectively not meeting eligibility criteria, 392 patients were allocated to the prednisone group and 393 patients to the placebo group.

Baseline characteristics of the two groups were well balanced (table 1). Median age of patients was 74 years, and 487 (62%) of 785 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. The appendix shows microbiological aetiology of community-acquired pneumonia, antibiotics given to patients, and supplemental data for clinical instability variables at baseline.

See Online for appendix

In the intention-to-treat analysis, median time to clinical stability was significantly shorter in the prednisone group (3·0 days; IQR 2·5–3·4) than in the placebo group (4·4 days; IQR 4·0–5·0) with an HR of 1·33 (95% CI 1·15–1·50, p<0·0001; figure 2 and table 2). Results for the per-protocol population were similar (table 2) and were confirmed by the adjusted analysis (appendix). We noted no evidence of effect modification in different prespecified subgroups based on median age, initial median CRP concentration, previous history of COPD, severity of community-acquired pneumonia defined by the PSI score (I–III *vs* IV–V), or blood culture positivity (appendix). We noted no significant effect modification in post-hoc analysis of patients with or without sepsis at randomisation (data not shown). However, we noted a trend towards a larger treatment effect in patients with sepsis.

Median time to effective discharge from hospital was shorter in the prednisone group than in the placebo group (table 2). The total duration of antibiotic treatment did not differ between groups, but duration of intravenous antibiotic treatment was lower in the prednisone group than in the placebo group. Rates of recurrent pneumonia, re-admission to hospital, and ICU admittance were similar in both treatment groups. All-cause mortality at day 30 did not differ between groups. The community-acquired pneumonia scores at day 5 and at day 30 did not differ between groups.

CRP concentrations were significantly lower in the prednisone group than in the placebo group on days 3, 5, and 7 (data not shown); PCT levels did not differ between treatment groups (data not shown).

Overall, complications associated with community-acquired pneumonia (ie, acute respiratory distress syndrome, empyema, respiratory failure with intubation, persistence of pneumonia, and mortality associated with community-acquired pneumonia) tended to be lower in the prednisone group than in the placebo group (table 3; appendix).

Incidence of any adverse events compatible with corticosteroid use was higher in the prednisone group than in the placebo group (table 3). This finding was due to a higher rate of in-hospital hyperglycaemia needing insulin treatment in the prednisone group than in the placebo group. The rates of new need for insulin treatment at day 30 were low in both groups. The incidence of other adverse events compatible with corticosteroid use was small and similar in both groups.

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			OR (95% CI) or difference (95% CI)	p value
Incidence of pneumonia-associated complications until day 30				
Complications due to community-acquired pneumonia, any	11 (3%)	22 (6%)	0·49 (0·23 to 1·02)	0·056
Acute respiratory distress syndrome	0	1 (<1%)		
Empyema	1 (0·3%)	5 (1%)		
Respiratory failure, intubation	1 (<1%)	6 (2%)		
Persistence of pneumonia	6 (2%)	5 (1%)		
Mortality associated with community-acquired pneumonia*	5 (1%)	7 (2%)		
Incidence of adverse events compatible with corticosteroid use until day 30				
Weight change, kg	–1·0 (–3·0 to 1·0)	–1·0 (–3·0 to 0·4)	Difference 0·34 (–0·56 to 1·25),	0·46
Adverse events, any	96 (24%)	61 (16%)	1·77 (1·24 to 2·52)	0·0020
In-hospital hyperglycaemia needing new insulin treatment	76 (19%)	43 (11%)	1·96 (1·31 to 2·93)	0·0010
New insulin dependence at day 30	5 (1%)	1 (<1%)		
New hypertension at day 30	6 (2%)	2 (1%)		
Delirium	5 (1%)	2 (1%)		
Gastrointestinal bleeding	3 (1%)	4 (1%)		
Nosocomial infections	13 (3%)	14 (4%)		
Other adverse events until day 30				
Any	20 (5%)	34 (9%)	0·57 (0·32 to 1·00)	0·052
Falls with fracture	0	4 (1%)		
Cardiac decompensation	5 (1%)	10 (3%)		
Cardiac event	6 (2%)	3 (1%)		
Acute stroke	2 (1%)	2 (1%)		
Thrombembolic event	0	3 (1%)		
Other	9 (2%)	12 (3%)		

Data are median (IQR) or number (%) unless otherwise stated. OR=odds ratio. *Mortality associated with community-acquired pneumonia was defined as death from community-acquired pneumonia or death from complications due to community-acquired pneumonia.

Table 3: **Complications and adverse events**

Discussion

In this trial, a 7-day treatment with prednisone in patients with community-acquired pneumonia led to a reduction in time to clinical stability of 1·4 days, to an overall reduction of length of hospital stay of 1 day, and to a reduction in duration of intravenous antibiotic treatment of 1 day. This effect seemed to be valid across all PSI classes and independent of age. Incidence of pneumonia-associated complications until day 30 tended to be lower in the prednisone group than in the placebo group. The prednisone group had a higher rate of inhospital hyperglycaemia needing insulin treatment than did the placebo group, whereas other adverse events compatible with corticosteroid use were rare and similar in both groups.

Pulmonary and circulating inflammatory cytokine concentrations are increased in patients with community-acquired pneumonia, serving as effective mechanism for the elimination of invading pathogens. Although initially beneficial, an unrestrained inflammatory condition might be detrimental.[3] Accordingly, non-survivors of community-acquired pneumonia show persistently increased concentrations of circulating inflammatory cytokines over time.[24] Corticosteroids are the most potent anti-inflammatory drugs, with which favourable effects were reported in patients with pneumococcal pneumonia from as early as 1955.[4] Our findings support the hypothesis that administration of corticosteroids modulates the

Panel: **Research in context**

Systematic review

We systematically searched PubMed using "community-acquired pneumonia" and "corticosteroids" for randomised, placebo-controlled trials or meta-analyses investigating the effects of corticosteroids as adjunctive therapy for community-acquired pneumonia. Language restrictions were not imposed. The last search was done on Dec 2, 2014. Recent systematic reviews and meta-analyses[9–13] suggest a possible benefit of adjunct corticosteroids for community-acquired pneumonia in severely ill patients, but with moderate disease severity, evidence is weak. The only two randomised placebo-controlled trials including 213 and 304 patients with pneumonia of any severity yielded controversial results. One study[7] did not find any benefit of adjunct corticosteroids, but an increased recurrence rate, the other[8] reported a reduction in length of hospital stay by 1 day.

Interpretation

Our trial with 785 patients shows that a 7-day course of 50 mg oral prednisone daily shortens time to clinical stability by 1·4 days in patients admitted for community-acquired pneumonia of any severity. Furthermore, time to hospital discharge and duration of intravenous antibiotic treatment are reduced by 1 day without an increase in complications associated with community-acquired pneumonia. When adding our study to previous evidence, a meta-analysis now shows a significant reduction of length of hospital stay (appendix). However, hyperglycaemia has to be anticipated, and the usual contraindications for corticosteroids must be taken into consideration.

immune response and thereby shortens time to clinical stability and length of hospital stay. Importantly, symptom resolution, reduction of length of hospital stay, and reduction of intravenous antibiotic therapy are relevant clinical goals in the treatment of patients with community-acquired pneumonia. The anti-inflammatory effect of prednisone treatment has a significant beneficial effect on these goals. This is not only relevant from a patient perspective, but is also an important determinant of hospital costs and efficiency.

Our results confirm data of various clinical trials (panel),[4–8,25–30] systematic reviews,[9,10] and meta-analyses[11–13] showing a beneficial effect of corticosteroids in community-acquired pneumonia. They are consistent with a randomised trial[8] comparing intravenous dexamethasone with placebo in 302 patients with community-acquired pneumonia outside the ICU, showing a similar reduction in length of hospital stay of 1 day as observed in our study. A small randomised trial with open-label design in 31 patients with community-acquired pneumonia of any severity comparing prednisolone for 3 days with placebo reported a reduction in hospital stay from 16 to 11 days. The small patient number might have been the reason for the non-significant results.[26]

Our results are in contrast to another randomised trial including 213 patients[7] showing that prednisolone once daily for a week did not improve clinical cure at day 7 nor length of hospital stay compared with placebo. However, when analysing these data without including patients directly admitted to the ICU, a significant reduction in time to clinical stability as well as an improvement in length of hospital stay of 1 day was noted.[31] This finding is unexpected, since it challenges the recent view that corticosteroids are beneficial for patients with severe community-acquired pneumonia in the ICU, but not indicated in patients with milder community-acquired pneumonia outside the ICU.[32] In our study, results remained similar with or without patients admitted to the ICU. It must be taken into account that patients in our cohort presented with community-acquired pneumonia of lower severity than that in previous studies.[7,8] More evidence on patients with severe community-acquired pneumonia in the ICU setting is expected by 2016 after completion of the ADRENAL trial (ClinicalTrials.gov, NCT01448109).

Irrespective of the inclusion or exclusion of patients with direct ICU admission in the analysis, the study by Snijders and colleagues[7] suggested more recurrences in the prednisolone group (20 [19%] of 104) than in the placebo group (10 [9%] of 109), raising concern about the occurrence of a rebound of inflammation after initial suppression by corticosteroids.[7] Our larger study could not confirm this finding, since rates of recurrence of pneumonia and re-admission to hospital were similar in the prednisone and placebo groups. A clinically relevant rebound phenomenon with an increased frequency of recurrent pneumonia seems therefore unlikely. The recurrence rate in our study was about 5% in both groups; considering the small absolute number of recurrences in the study by Snijders and colleagues, their finding of slightly more recurrences with corticosteroids is probably attributable to chance.

Other pneumonia-associated complications in our study such as incidence of empyema, acute respiratory distress syndrome, or respiratory failure were low and tended to be higher in the placebo group than in the prednisone group.

Hyperglycaemia needing insulin treatment during hospital admission was higher in the prednisone group than in the placebo group, similar to the study by Meijvis and colleagues.[8] This increased hyperglycaemia did not, however, affect the clinical outcome and did not prolong hospital stay. Moreover, the number of patients with new need for insulin treatment at day 30 was low. Other adverse events compatible with corticosteroid use in our study were rare, and the incidence did not differ between groups. We assume that the short exposure to corticosteroids, when they

are not tapered off during several days but stopped abruptly after 7 days, has a favourable effect on corticosteroid-associated complications.

We did not note any effect modification in different prespecified subgroups based on median age, initial median CRP, previous history of COPD, severity of community-acquired pneumonia defined by the PSI score, or blood culture positivity. In a post-hoc analysis, we noted a trend towards a larger treatment effect in patients with sepsis. Furthermore, a positive treatment response to prednisone was not restricted to patients with a specific aetiological diagnosis, but was seen irrespective of the identified microorganism.

Our study has several strengths as compared with previous studies. First, it is the largest and thus most conclusive randomised placebo-controlled trial of corticosteroids in community-acquired pneumonia including more than 800 patients; this gave the study sufficient power to show a difference in time to clinical stability and length of hospital stay. Second, patients with all severity classes of community-acquired pneumonia were included, representing daily routine in patients admitted to hospital with community-acquired pneumonia. However, the sickest patients (eg, patients in the ICU and patients with sepsis) were under-represented. In these patients, the current guidelines of the Surviving Sepsis Campaign[2] regarding the indication for glucocorticoids should be applied. Finally, we used an oral dose of prednisone, which is easier to apply to patients with community-acquired pneumonia compared with intravenous doses of dexamethasone, applied in an earlier trial.[8]

Our study has also limitations. First, we exclusively included patients admitted to hospital, which precludes a generalisation to patients in ambulatory care. Second, our study was not powered for mortality; therefore, mortality data have to be acknowledged with care. Third, our primary endpoint, time to clinical stability, has limitations, since it is a combined endpoint including several parameters; however, it is a well accepted and frequently used endpoint in patients with community-acquired pneumonia.[33] Finally, corticosteroid-induced hyperglycaemia might have led to unblinding in some patients.

Contributors

CAB, MB, BM, and MC-C designed the study and wrote the protocol. CAB, NN, EU, IS-W, BW, RB, HE, DD, BA, SAU, JR, PT, SW, RT, CB, HD, and NR recruited patients for the study and participated in coordination. CAB, NN, PS, MB, and MC-C had access to all the data, analysed the data, were responsible for the decision to submit the report, and drafted it. PS, RB, WZ, PT, DB, NR, BM, and MC-C participated in coordination, gave financial and staff support, and critically revised the report. All authors read and approved the final report.

Declaration of interests

We declare no competing interests.

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