Strategies to optimise the treatment of community-acquired pneumonia

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CHAPTER 2

Adjunctive treatment with oral dexamethasone in non-ICU patients hospitalised with community-acquired pneumonia: A randomised clinical trial

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ABSTRACT

Background

Adjunctive intravenous corticosteroid treatment has been shown to reduce length of stay (LOS) in adults hospitalised with community-acquired pneumonia (CAP). We aimed to assess the effect of oral dexamethasone on LOS and whether this effect is disease severity dependent.

Methods

In this multicentre, stratified randomised, double-blind, placebo-controlled trial, immunocompetent adults with CAP were randomly assigned (1:1 ratio) to receive oral dexamethasone (6 mg once daily) or placebo for 4 days in four teaching hospitals in the Netherlands. Randomisation (blocks of four) was stratified by CAP severity (pneumonia severity index class I–III and IV–V). The primary outcome was LOS.

Results

Between December 2012 and November 2018, 401 patients were randomised to receive dexamethasone (n=203) or placebo (n=198). Median LOS was shorter in the dexamethasone group (4.5 days, 95% CI 4.0–5.0 days) than in the placebo group (5.0 days, 95% CI 4.6–5.4 days; p=0.033). Within both CAP severity subgroups, differences in LOS between treatment groups were not statistically significant. The secondary ICU admission rate was lower in the dexamethasone arm (5 (3%) versus 14 (7%); p=0.030); 30-day mortality did not differ between groups. In the dexamethasone group the rate of hospital readmission tended to be higher (20 (10%) versus 9 (5%); p=0.051) and hyperglycaemia (14 (7%) versus 1 (1%); p=0.001) was more prevalent.

Conclusion

Oral dexamethasone reduced LOS and ICU admission rate in adults hospitalised with CAP. It remains unclear for which patients the risk–benefit ratio is optimal.

INTRODUCTION

Despite advances in antibiotic treatment and the availability of preventative measures such as vaccines, the burden of community-acquired pneumonia (CAP) remains high.[1] Therefore, nonantibiotic adjunctive therapies that modify the host response to microorganisms remain of interest.[2]

Excessive release of cytokines in response to invading pathogens is thought to contribute to high mortality and morbidity in patients with CAP.[3] Corticosteroids can inhibit inflammation by downregulating this cytokine response.[4] Through this mechanism, adjunctive treatment with corticosteroids might improve clinical outcomes.

Several randomised controlled trials (RCTs) show that adjunctive corticosteroid treatment reduces hospital length of stay (LOS).[5] However, most RCTs have studied intravenous corticosteroid treatment. Dexamethasone administered intravenously during the first 4 days of hospitalisation has been shown to reduce LOS by 1 day.[6] Oral administration of dexamethasone has several advantages over iv administration. It does not hamper an early iv-to-oral switch of antibiotics, causes patients less discomfort and carries no risk of phlebitis. Furthermore, a bioequivalence study showed that oral dexamethasone is feasible from a pharmacokinetics perspective.[7] Thus, we opted to investigate the effect of oral dexamethasone in patients with CAP.

Moreover, it is still debated which patients benefit most from corticosteroid treatment.[8] A recent individual patient data meta-analysis (IPDMA) suggested a greater effect of corticosteroids in patients with severe CAP, defined by a high pneumonia severity index (PSI) score.[5] So far, no RCT has prospectively investigated the effects of corticosteroids in pre-specified subgroups based on CAP severity.

The primary objective of this study was to investigate the effect of a short course of oral dexamethasone compared with placebo on LOS and to assess whether this effect depends on disease severity.

MATERIALS AND METHODS

Study design and patients

This multicentre, stratified randomised, double-blind, placebo-controlled trial was conducted in four non-academic teaching hospitals in the Netherlands. Patients presenting with CAP were screened and enrolled within 24 h of emergency department presentation. Inclusion criteria were age ≥18 years and the presence of new opacities on chest radiography, and two of the following signs and symptoms: cough, production of sputum, temperature >38.0°C or <36.0°C, abnormalities at auscultation consistent with pneumonia, C-reactive protein (CRP) >15 mg/L, white blood cell count >10×10^9 or <4×10^9 cells/L, or >10% of bands in leukocyte differentiation. The following patients were excluded from study participation: patients with a congenital or acquired immunodeficiency, patients treated with chemotherapy <6 weeks prior to emergency department presentation, patients receiving corticosteroids or other immunosuppressive medication 6 weeks prior to emergency department presentation, patients requiring direct admission to the intensive care unit (ICU) at hospital presentation, patients with a known tropical worm infection, pregnant or breastfeeding females and patients with an intolerance for dexamethasone. Patients opting for palliative care, who did not receive active treatment for pneumonia, were also not eligible for study participation. All other patients with limitations in treatment (e.g. those who did not wish to be resuscitated, or did not want to be admitted to the ICU if necessary, or those who did not wish to be intubated) but who did seek active treatment for the pneumonia were eligible for study participation. Written informed consent was provided by all patients. This study was approved by the Medical Ethics Committee at St Antonius Hospital (Nieuwegein, The Netherlands) and is registered at ClinicalTrials.gov with identifier number NCT01743755.

Eligible patients were randomly allocated (1:1 ratio) to receive either 6 mg oral dexamethasone or placebo once a day for 4 days. A previous pharmacokinetics study showed that 6 mg dexamethasone orally equals the exposure of 5 mg dexamethasone phosphate (=4 mg dexamethasone) iv, as studied in the Ovidius trial.[6,7] Randomisation was performed in blocks of four using PASW Statistics software version 18.0.03 (IBM, Armonk, NY, USA). Patients were stratified by enrolling centre and by CAP severity (non-severe CAP and severe CAP). Non-severe CAP was defined as PSI class I–III and severe CAP was defined as PSI class IV–V.[9] Randomisation was set up to ensure that in each CAP severity subgroup, 50% of patients received dexamethasone and 50% of patients received placebo. After randomisation, patients were assigned a medication kit number using a central computer-assisted allocation system. Corresponding coded medication kits containing four tablets of 6 mg dexamethasone or placebo were available at the emergency department of each of the participating hospitals. Patients, treating physicians and investigators were masked to treatment allocation.

Methods

Patients in the dexamethasone group received 6 mg oral dexamethasone (Tiofarma, Oud-Beijerland, The Netherlands) once a day for 4 days and patients in the placebo group received one placebo tablet (Tiofarma) once a day for 4 days. Study treatment was initiated within 24 hours of emergency department presentation. Baseline blood samples for blood chemistry testing and haematology were obtained before initiation of study treatment in the emergency department as part of standard care. Measurements included CRP, electrolytes, glucose, renal function and a complete blood count. All patients received antibiotics prior to starting study medication. Decisions regarding antibiotic type, route of administration and treatment duration were made by the treating physician, and were based on Dutch national guidelines.[10,11] Microbiological testing included sputum cultures, blood cultures, PCR assays for respiratory viruses and atypical pathogens, and urinary antigen tests for the detection of *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae*. The decision to transfer a patient to the ICU or to discharge a patient was made by the treating physician. The general rule for discharge in all hospitals was that patients were clinically stable (improvement of shortness of breath, consistent decrease in CRP concentrations, absence of hyperthermia or hypothermia, adequate oral intake and adequate gastrointestinal absorption) and in well enough condition to leave the hospital. Baseline characteristics included medical history and variables necessary to calculate the PSI score.[9]

Analysis

The primary outcome was LOS measured in 0.5 days. LOS was calculated from time of emergency department presentation to the day of discharge, day of death or day of ICU admission (study medication was stopped after ICU admission because patients are regularly treated with corticosteroids in the ICU). If the patient was admitted to the emergency department before 12:00, the day of presentation was counted as 1 day. If the patient was admitted to the emergency department after 12:00, the day of presentation was counted as 0.5 days. The discharge date was defined as the date that a patient was medically ready for discharge (hereby excluding waiting time for admission to a nursing home). Time of discharge was set at 12:00 for all patients as patients are generally discharged late morning or early afternoon depending on ward logistics. Secondary outcomes were admission to the ICU after initial admission to the general ward and all-cause mortality within 30 days of hospital admission.

Sample size estimation was based on our hypothesis that dexamethasone could reduce the median LOS in all patients with CAP by 1 day and reduce the median LOS in patients with severe CAP by 2 days. With sample data pseudo-randomly generated from available data from our previous trial[6] and assuming that 50% of patients have severe CAP, it was simulated that 300 patients were needed in each arm to provide >80% power maintaining a type I error rate of 0.05 (two-sided).

The primary analysis was a Kaplan-Meier analysis of time to discharge. The Kaplan-Meier method was used to estimate the median LOS with 95% confidence interval for each treatment group and to assess the difference in LOS between treatment groups by analysing time to discharge. Patients who died, who were transferred to a different hospital or who were admitted to the ICU after study enrolment were censored to show that time of reporting was cut off before the event of interest for the primary analysis (i.e. hospital discharge) occurred. Because the intervention was a short course of oral dexamethasone, a Gehan-Breslow-Wilcoxon test was used for the Kaplan–Meier method as this test emphasises early differences.[12] Furthermore, we performed an extra sensitivity analysis in which patients who were admitted to the ICU after study enrolment were included in the time to discharge analysis.

To adhere to CONSORT (Consolidated Standards of Reporting Trials) guidelines on reporting results of randomised clinical trials we also calculated the unadjusted hazard ratio (HR) for discharge with 95% confidence interval using a Cox proportional hazards regression.[13] Differences in secondary outcomes between treatment groups were analysed with a Chi-squared test and risk ratios were calculated; a two-tailed p-value <0.05 was deemed significant. Statistical analyses were performed using SPSS version 24.0 (IBM). The primary analysis was performed according to the intention-to-treat principle after which the analysis was repeated in the per-protocol population. Patients who missed one or more doses of study medication while admitted to the general ward, whose diagnosis was altered, with exclusion criteria unknown at the time of study entry, or who were discharged on the day of study entry were excluded from the per-protocol analysis. The following predefined subgroup analyses were performed: 1) CAP severity (non-severe CAP versus severe CAP), 2) initial CRP level at emergency department presentation (above median versus below median) and 3) *S. pneumoniae* urinary antigen test result.

We added a sensitivity analysis to explore the effect of dexamethasone on hospital utilisation. The difference in hospital utilisation between treatment groups was assessed using a 30-day hospital-free approach (equivalent to the mechanical ventilator-free days approach). Hospital-free days (HFDs) were calculated by adding the number of days a patient was hospitalised during readmission (if a readmission occurred within 30 days of initial hospital admission) to the duration of initial hospital stay (including ICU admission) and subtracting this number from 30 days. If a patient died in hospital within 30 days of admission, the number of HFDs was 0. If a patient was not discharged within 30 days of admission, the number of HFDs was also 0. Because the effect of dexamethasone is primarily through shortened LOS rather than mortality, a Mann-Whitney U test was used to compare HFDs between groups.[14]

Categorical variables are shown as number (percentage). Continuous variables are presented as median (interquartile range (IQR)) or mean with standard deviation for variables with a nonparametric or parametric distribution, respectively.

Interim analyses to monitor the frequency of serious side-effects related to either dexamethasone or placebo were pre-planned at 200, 400 and 500 patients. The analyses and the review of the results were performed by an external independent Data Safety and Monitoring Board.

RESULTS

From 23 December 2012 to 28 November 2018, 1092 patients were screened for eligibility. For one hospital, screening logs were not available. 412 patients were randomly allocated to receive either dexamethasone or placebo; 11 patients were excluded post-randomisation (Figure 1). The study was prematurely terminated after the second interim analysis due to a slower inclusion rate than anticipated combined with a shorter LOS than used in our sample size calculation. Therefore, we did not expect a different outcome for LOS at 600 patients. Furthermore, for 30-day mortality we anticipated a 50% lower mortality rate in patients with severe CAP in the dexamethasone group compared with the placebo group (7.5% versus 15% based on results of an earlier trial).[6] Because there was no difference in 30-day mortality between treatment groups at 400 patients and the 30-day mortality was already lower than anticipated, we also did not expect a different outcome for 30-day mortality at 600 patients. The independent Data Safety and Monitoring Board found no grounds for early termination based on safety concerns.

There was no difference in baseline characteristics between the intervention and placebo groups (Table 1). The mean (±SD) PSI score calculated for all patients was 81±29. The severe CAP subgroup consisted of 156 (39%) patients. There was no difference in the distribution of causative organisms and initial antibiotic treatment between treatment groups (Supplementary Tables E1 and E2).

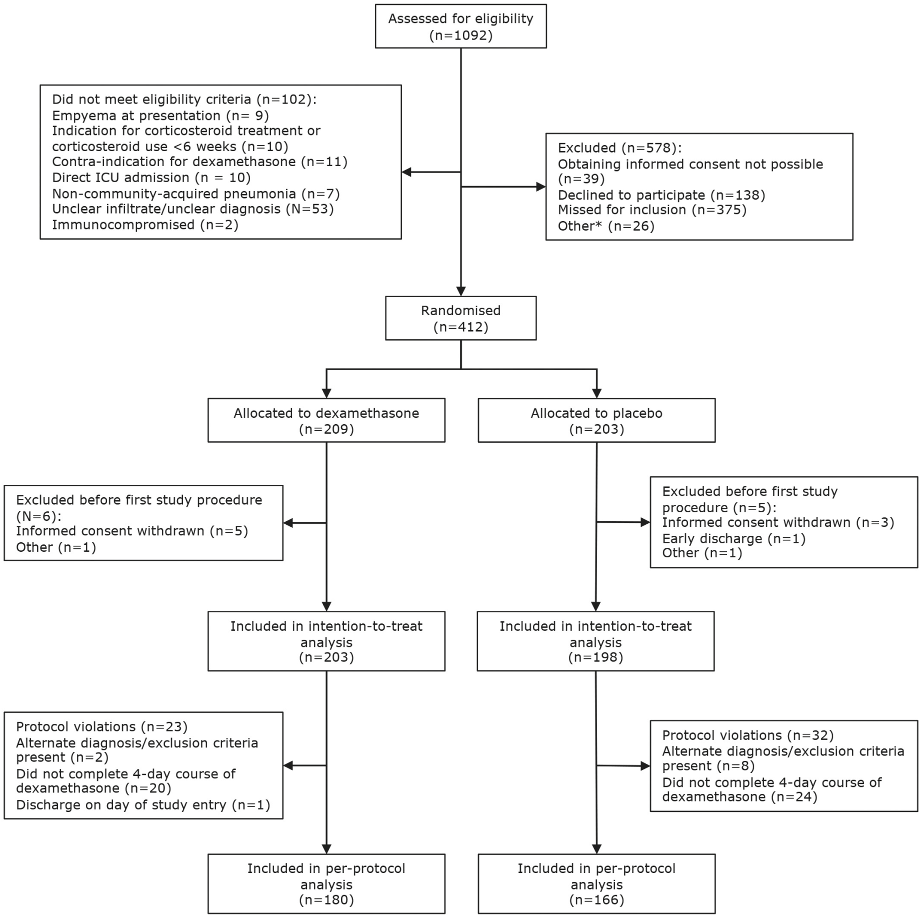


Figure 1 Study profile. No patient was lost to follow-up before reaching the primary endpoint. ICU: intensive care unit. *: e.g. transferred to another hospital or patient opting for palliative care.

Table 1 Baseline characteristics of enrolled patients

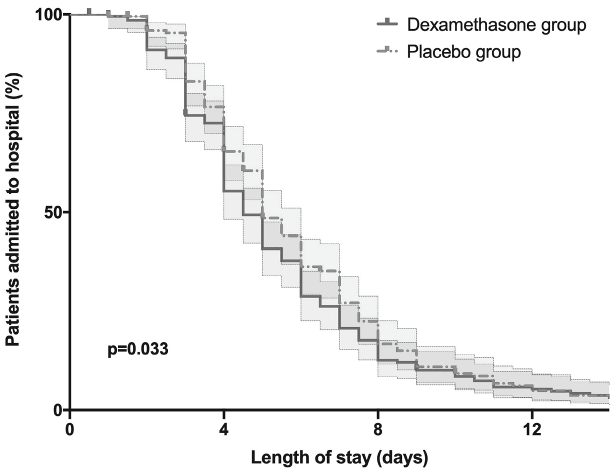
	All patients		PSI I-III		PSI IV-V	
	Placebo (n=198)	**Dexamethasone (n =203)**	**Placebo (n=119)**	**Dexamethasone (n = 126)**	**Placebo (n=79)**	**Dexamethasone (n =77)**
Men	120 (61)	116 (57)	58 (49)	63 (50)	62 (79)	53 (69)
Age (years)	67 [54-76]	68 [57-76]	61 [44-69]	61 [50-70]	77 [68-83]	76 [69-83]
Ethnicity						
Caucasian	186 (94)	197 (97)	111 (93)	122 (97)	75 (95)	75 (97)
Other	11 (6)	6 (3)	7 (6)	4 (3)	4 (5)	2 (3)
Elderly home resident	1 (1)	6 (3)	0 (0)	2 (2)	1 (1)	4 (5)
Current smoker	45 (23)	53 (26)	26 (22)	39 (31)	19 (24)	14 (18)
Antibiotic treatment prior to admission	57 (29)	56 (28)	40 (34)	35 (28)	17 (22)	21 (27)
Comorbidities						
Neoplastic disease	6 (3)	8 (4)	1 (1)	0 (0)	5 (6)	8 (10)
Liver disease	2 (1)	2 (1)	1 (1)	1 (1)	1 (1)	1 (1)
Congestive heart failure	17 (9)	20 (10)	4 (3)	4 (3)	13 (17)	16 (21)
Renal disease	27 (14)	32 (16)	6 (5)	7 (6)	21 (27)	25 (33)
Diabetes Mellitus	47 (24)	41 (20)	14 (12)	22 (18)	33 (42)	19 (25)
COPD	35 (18)	40 (20)	20 (17)	22 (18)	15 (19)	18 (23)
Physical examination findings						
Temperature (°C)	38.3 (1.2)	38.4 (1.1)	38.3 (1.1)	38.4 (0.9)	38.3 (1.3)	38.4 (1.3)
SBP (mmHg)	128 (22)	130 (22)	127 (20)	131 (18)	121 [112-147]	130 [104-148]
Heart rate (bpm)	98 [87-110]	99 [87-111]	98 [90-110]	100 [90-111]	98 (20)	98 (23)
Resp rate (breaths/min)	20 [18-25]	20 [16-25]	21 (5)	20 (5)	23 (7)	23 (7)
Blood oxygen saturation	93.6 (4.1)	93.7 (4.2)	94.6 (3.7)	94.1 (4.4)	92.2 (4.2)	93.0 (3.6)
Altered mental status	14 (7)	13 (6)	0 (0)	1 (1)	14 (18)	12 (16)

Table 1 Continued

	All patients		PSI I-III		PSI IV-V	
	Placebo (n=198)	**Dexamethasone (n =203)**	**Placebo (n=119)**	**Dexamethasone (n = 126)**	**Placebo (n=79)**	**Dexamethasone (n =77)**
Inflammatory parameters						
CRP (mg/L)	198 [82-309]	211 [86-330]	190 [84-291]	249 [131-336]	203 [61-323]	153 [41-314]
WBC (10^9 cells/L)	13.0 [9.7-17.5]	13.7 [10.1-18.2]	13.0 [9.6-17.6]	14.0 [10.3-19.0]	13.0 [9.7-17.1]	13.1 [9.4-17.5]
PSI score	82 (29)	81 (29)	69 [52-76]	65 [52-76]	106 [97-115]	106 [97-120]
PSI risk class						
Class 1	25 (13)	27 (13)	25 (21)	27 (21)	-	-
Class 2	40 (20)	55 (27)	40 (34)	55 (44)	-	-
Class 3	54 (27)	44 (22)	54 (45)	44 (35)	-	-
Class 4	70 (35)	64 (31)	-	-	70 (90)	64 (82)
Class 5	9 (5)	13 (6)	-	-	9 (11)	13 (17)

Data are presented as n (%), median (interquartile range) or mean (±SD). PSI: pneumonia severity index; COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; Resp rate: respiraoty rate; CRP: C-reactive protein; WBC: white blood cell.

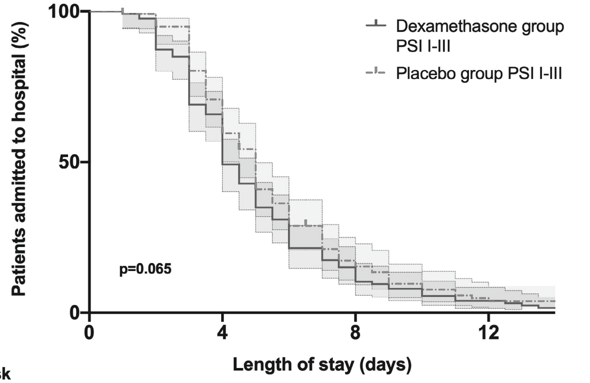
In the intention-to-treat population, Kaplan-Meier analysis showed that median LOS was 0.5 days shorter in the dexamethasone group (4.5 (95% CI 4.0–5.0) days) than in the placebo group (5.0 (95% CI 4.6– 5.4) days) (Table 2). Kaplan-Meier analysis of time to discharge showed a significant difference between treatment groups (p=0.033) (Figure 2). Although non statistically significant, in the non-severe CAP subgroup LOS was 1.0 day shorter in the dexamethasone group compared with the placebo group (Table 2 and Figure 3). There was no difference in LOS between treatment groups in the severe CAP subgroup (Table 2 and Figure 3). Results were similar in the per-protocol population (Supplementary Table E3). In the Kaplan-Meier analysis in which ICU patients were not censored, median LOS was 5.0 (95% CI 4.5– 5.5) days in the dexamethasone group and 5.5 (95% CI 5.0–6.0) days in the placebo group (p=0.012) (Supplementary Figure E1). Using Cox regression, HR for discharge was 1.14 (95% CI 0.93–1.39) for all patients, 1.19 (95% CI 0.92–1.54) in the mild pneumonia group and 1.06 (95% CI 0.76–1.48) in the severe pneumonia group.



Number at risk

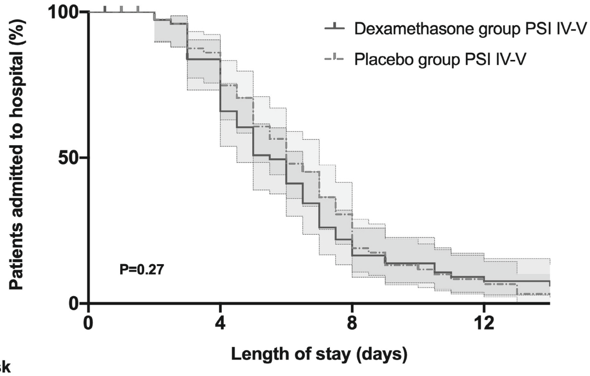
Dexamethasone group	203	144	35	11
Placebo group	198	143	39	10

Figure 2 Kaplan–Meier analysis of the effect of dexamethasone on hospital length of stay in all enrolled patients. Patients who were admitted to the intensive care unit and/or died in hospital (n=21) and patients who were transferred to another hospital (n=2) were censored on the day of admission to the intensive care unit, day of death or day of transfer. The shading represents the confidence bands.



Number at risk

Dexamethasone group	126	83	19	5
Placebo group	119	82	18	5



Number at risk

Dexamethasone group	77	61	16	6
Placebo group	79	61	21	5

Figure 3 Kaplan–Meier analysis of the effect of dexamethasone on hospital length of stay stratified according to community-acquired pneumonia severity. Patients who died, were admitted to the intensive care unit or were transferred to a different hospital were censored on the day of death, day of admission to the intensive care unit or day of transfer. The shading represents the confidence bands.

For secondary outcomes, the secondary ICU admission rate was lower in the dexamethasone group (n=5 (3%)) than in the placebo group (n=14 (7%); p=0.030). Respiratory failure was the most common reason for ICU admission (Supplementary Table E5). The 30-day mortality rate did not differ between both treatment groups (Table 2). Causes of death are shown in Supplementary Table E6. The aforementioned results for the intention-to-treat population were similar in the per-protocol population (Supplementary Table E3). Results of predefined subgroup analyses are presented in Supplementary Table E4.

Table 2 Overview of primary and secondary end-points for the intention-to-treat population

	Dexamethasone[#] N = 203	Placebo[¶] N = 198	Risk ratio (95% CI)	p-value
Hospital LOS days				
All patients	4.5 (4.0–5.0)	5.0 (4.6–5.4)	-	0.033[+]
PSI class I-III	4.0 (3.6–4.4)	5.0 (4.5–5.5)	-	0.065[+]
PSI class IV-V	5.5 (4.6–6.4)	6.0 (5.1–6.9)	-	0.27[+]
Secondary ICU admission				
All patients	5 (3)	14 (7)	0.35 (0.13–0.95)	0.030[§]
PSI class I-III	0 (0)	6 (5)	-	0.011[§]
PSI class IV-V	5 (7)	8 (10)	0.64 (0.22–1.87)	0.41[§]
30-day mortality				
All patients	4 (2)	7 (4)	0.56 (0.17–1.87)	0.34[§]
PSI class I-III	1 (1)	2 (2)	0.47 (0.04–5.14)	0.53[§]
PSI class IV-V	3 (4)	5 (6)	0.62 (0.15–2.49)	0.49[§]

Data are presented as n, median (95% CI) or n (%), unless otherwise stated. LOS: length of stay; PSI: pneumonia severity index; ICU: intensive care unit. [#]: PSI class I–III n=126, PSI class IV–V n=77; [¶]: PSI class I–III n=119, PSI class IV–V n=79; [+]: Gehan–Breslow–Wilcoxon test; [§]: Chi-squared test.

Adverse events are shown in Table 3. The readmission rate within 30 days of study entry was higher in the dexamethasone group compared with the placebo group (20 (10%) versus 9 (5%); p=0.051). Reasons for readmission are shown in Supplementary Table E7. The median (IQR) number of HFDs was 25.0 (22.0– 26.0) in the dexamethasone group and 24.5 (22.5–26.5; p=0.061) in the placebo group. Hyperglycaemia was reported by physicians in 14 (7%) patients in the dexamethasone group and one (1%) patient in the placebo group (p=0.001). In the placebo group, one patient had a newly diagnosed myxoma and one patient was diagnosed with HIV. Both were transferred to an academic hospital. In the dexamethasone group, one patient had a perforated jejunal diverticulitis requiring surgical intervention. Abdominal complaints were present before study entry. Furthermore, in the dexamethasone group three patients had an ischaemic cerebrovascular accident and one patient developed deep venous thrombosis of the right leg.

Table 3 Overview of adverse events

	Dexamethasone N = 203	Placebo N = 198	Risk ratio (95% CI)	p-value[+]
Adverse event				
Readmission[#]	20 (10)	9 (5)	2.09 (0.98–4.47)	0.051
Empyema	3 (2)	5 (3)	0.59 (0.14–2.42)	0.45
Hyperglycaemia	14 (7)	1 (1)	13.7 (1.81–103)	0.001
Neuropsychiatric complaints (e.g. delirium, agitation)	10 (5)	7 (4)	1.39 (0.54–3.59)	0.49
Cardiac events (e.g. arrhythmia, congestive heart failure, myocardial infarction)	9 (4)[¶]	4 (2)	2.19 (0.69–7.01)	0.17

Data are presented as n or n (%), unless otherwise stated. [#]: n=201 patients analysed in the dexamethasone group and n=189 patients analysed in the placebo group (excluding missing (n=2) and patients who died in hospital (n=9)); [¶]: one patient suffered myocardial infarction and was admitted to the cardiac ward, and one patient was admitted to the cardiac ward after discharge due to ongoing angina pectoris and fatigue; [+]: Chi-squared test.

DISCUSSION

In the primary analysis of this trial, we observed a reduction in median LOS of 0.5 days in patients with CAP treated with oral dexamethasone compared with controls.

This finding supports our hypothesis that dexamethasone reduces LOS in patients with CAP. However, a 0.5-day reduction is lower than the hypothesised 1-day reduction. It is also lower than reported by Briel et al.[5] who also found a 1-day reduction of LOS in their IPDMA of six trials. The median LOS in our study was shorter compared with all trials included in the IPDMA by Briel et al.[5], which may explain the difference in absolute reduction in LOS. Still, the relative reduction in LOS was 10% in our trial compared with 12.5% found by Briel et al.[5] Thus, the relative effect of dexamethasone on LOS in our study was similar. The difference in overall LOS could be explained by the fact that most studies in the IPDMA used iv study medication; this may have hampered early iv-to-oral antibiotic switch and consequently an earlier discharge. Furthermore, there were fewer patients with severe CAP in our trial compared with the two trials in the IPDMA with similar inclusion criteria (39% versus 47% and 49%).[6,15]

The Cox regression analysis did not show a statistically significant difference in time to discharge between treatment groups. This analysis was included to adhere to CONSORT guidelines on reporting clinical trial results. However, the Cox regression requires the assumption of proportional hazards. Because we investigated a short course of dexamethasone and most patients were discharged during the first 5 days of hospital admission, the assumption of proportional hazards is not met.

This is the first study to show a reduction in the rate of secondary ICU admissions in patients with CAP receiving corticosteroids. However, as respiratory failure was the main reason for ICU admission (n=14 (74%)), this finding is in line with the meta-analysis by Stern et al.[16] who showed a lower risk of new respiratory failure in patients receiving corticosteroids. In line with the IPDMA by Briel et al.[5], we did not observe a beneficial effect of corticosteroids on 30-day mortality. Stern et al.[16] did show a beneficial effect of corticosteroids on mortality. However, in that meta-analysis, small studies with an unclear allocation concealment were mainly responsible for that finding.[17–19]

Contrary to our hypothesis, we did not observe a beneficial effect of dexamethasone in patients with severe CAP. The beneficial effects of dexamethasone seemed greater in the non-severe CAP subgroup. In the latter group, no patients receiving dexamethasone were admitted to the ICU and the median LOS was 1.0 day shorter in patients receiving dexamethasone compared with those receiving placebo (although not statistically significant). It is difficult to draw conclusions due to the relatively small number of patients in each subgroup. However, it is still interesting to explore this counterintuitive finding. It could be related to the fact that we used the PSI score to define severe CAP. The PSI score is a good predictor of mortality, yet the PSI score does not necessarily correspond with the level of inflammation. The PSI score is mainly influenced by age and the presence of comorbidities. We therefore performed an additional explorative analysis using the CURB-65 (confusion, urea >7 mmol/L, respiratory rate ≥30 breaths/min, blood pressure <90 mmHg (systolic) or ≤60 mmHg (diastolic), age ≥65 years) score. The CURB-65 score is based on clinical parameters; it does not include comorbidities and is less influenced by age than the PSI score. Indeed, we found the largest LOS reduction in patients aged <65 years with high CURB-65 scores (≥2 points) (Supplementary Figure E2). Furthermore, in our predefined subgroup analysis dexamethasone reduced LOS and the rate of secondary ICU admission in patients with a CRP above the median. We did not find this effect in patients with a CRP below the median. Two post hoc analyses of RCTs investigating corticosteroids in CAP have also noted that patients with a high level of inflammation benefitted most from corticosteroids. Remmelts et al.[20] previously observed that dexamethasone was most effective in patients with a high level of pro-inflammatory cytokines combined with discrepantly low cortisol levels. Urwyler et al.[21] found that only a high level of pro-inflammatory cytokines predicted a positive response to steroids. Consequently, a prediction score based solely on the level of inflammation is of interest as it might aid in identifying the subgroup of patients that would benefit most from dexamethasone.

Regarding safety, the rate of patients readmitted within 30 days of admission was twice as high in the dexamethasone group compared with the placebo group (5% versus 10%; number needed to harm n=20). However, this difference did not reach statistical significance. The rate of hyperglycaemia was higher in the dexamethasone group, which is in line with the pharmacology of corticosteroids and with an earlier trial.[6]

Our study has several strengths. First, it is the second largest multicentre trial assessing the effects of corticosteroids in patients with CAP and it is the first trial to use stratified randomisation to assess the effects of corticosteroids within subgroups based on CAP severity. Second, a short course of oral dexamethasone has several advantages over longer courses of iv administered corticosteroids.

There were several limitations to this study. First, the results cannot be generalised to all patients with CAP. Patients admitted directly to an ICU (i.e. the most critically ill patients) were excluded. Second, the trial was prematurely terminated due to slower inclusion rates than anticipated. The results of the interim review of the study's data at 400 patients showed a shorter LOS compared with our sample size calculation and therefore we do not expect a different outcome for LOS at 600 patients. Furthermore, because 30-day mortality was lower than anticipated and because there was no difference in 30-day mortality between treatment groups at 400 patients, we would not expect different findings if the planned 600 patients would have been included. Last, the number of patients reported to have hyperglycaemia is substantially lower than described by Briel et al.[5] We cannot exclude the possibility of underreporting as the presence of hyperglycaemia was based on voluntarily reporting by research physicians instead of a structured assessment. Glucose was measured on day 4, a time when many patients were already discharged. In hindsight, this might limit an all-inclusive benefit–risk assessment. However, the relative risk was similar to other studies.

The benefits of dexamethasone should be weighed against the risks. A 10% reduction in LOS and reduction in ICU admissions seems to be a considerable benefit for patients. However, this should be weighed against a possible rise in readmissions. The sensitivity analysis using HFDs showed a small (statistically nonsignificant) difference between treatment groups in favour of dexamethasone. It seems that corticosteroid treatment does not benefit all patients with CAP. Therefore, it is important to identify subgroups of patients who benefit most and/or suffer least from corticosteroid treatment. High levels of inflammatory biomarkers such as cytokines, procalcitonin, pro-adrenomedullin and a high neutrophil/lymphocyte ratio have been associated with unfavourable outcomes in CAP.[21–23] In other studies, only measurement of inflammation based on cytokine levels has been shown to predict response to corticosteroids. In the present study we found that dexamethasone had a greater effect in patients with a high CRP. Future research is necessary to determine how CRP and other inflammatory biomarkers can predict response to corticosteroids, preferably using readily available biochemical tests that provide fast results.

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SUPPLEMENTARY MATERIAL

Supplementary Table E1 Etiological diagnosis for all enrolled patients

	Placebo Group (n=198)	Dexamethasone group (n=203)
Streptococcus pneumoniae	35 (18)[1]	40 (20)[2]
Legionella spp.	15 (8)[3]	12 (6)[4]
Haemophilus influenzae	8 (4)[5]	7 (3)[6]
Mycoplasma pneumoniae	6 (3)	6 (3)
Chlamydia psittaci	4 (2)	2 (1)
Staphylococcus aureus	4 (2)[7]	1 (0)[8]
Influenza A/B virus	9 (5)[9]	8 (4)
Other pathogen*	3 (2)[10]	5 (2)[11]
Other viruses‡	5 (3)	6 (3)
Unidentified	109 (55)	116 (57)

*Other pathogens: *Coxiella burnetti*, *Pneumocystis jiroveci*, *Escheria coli*, group A streptococci, *Haemophilus haemolyticus*, *chlamydia pneumoniae*, *Neisseria meningitidis*
‡Other virusses: Parainfluenza virus, Rhinovirus, Respiratory synctiel virus, human metapneumovirus (hMPV).
[1]Mixed infection with: influenza A virus (n=1), *Moraxella catarrhalis* (n= 1), hMPV (n=1), Rhinovirus (n=2), *H. influenzae* (n = 1), *H. influenza* and Rhinovirus *(n=1).*
[2]Mixed infection with: *S. aureus* (n=1), Influenza type A (n=2), *H. influenza* (n=1), *E. coli* (n=1)
[3]Mixed infection with: hMPV (n=1), Influenza type B (n=1)
[4]Mixed infection with: *S. pneumoniae* (n=1)
[5]Mixed infection with: *S. aureus* (n=2), Influenza type A (n=1)
[6]Mixed infection with: *Klebsiella pneumoniae* and *E. coli* (n=1), Influenza type A virus (n=2)
[7]Mixed infection with: *Pseudomonas aeruginosa* and Rhinovirus (n=1)
[8]Mixed infection with: Rhinovirus (n=1)
[9]Mixed infection with: *Candida albicans* (n=1)
[10]Mixed infection with: Rhinovirus (n=1), *M .pneumoniae* (n=1)
[11]Mixed infection with: Rhinovirus (n=1)

Supplementary Table E2 Initial antibiotic regimen at time of hospital admission

	Dexamethasone group (n= 203)	Placebo group (n= 198)
Penicillin monotherapy*	81 (40)	80 (40)
Cephalosporin monotherapy	31 (15)	28 (14)
Fluoroquinolone, macrolide or doxycycline monotherapy	5 (3)	10 (5)
Penicillin combined with a fluoroquinolone, macrolide or doxycycline	38 (19)	37 (19)
Cephalosporin combined with a fluoroquinolone, macrolide or doxycycline	36 (18)	32 (16)
Other	10 (5)	10 (5)
Unknown	2 (1)	1 (1)

Data are number (%). *Penicillin, amoxicillin or amoxicillin/clavulanic acid.

Supplementary Table E3 Overview of primary and secondary endpoints for the per-protocol population.

Endpoint	**Dexamethasone (n=180)**	**Placebo (n=166)**	**risk ratio (95% CI)**	**p-value**
Length of stay (days)				
All patients	4.5 (4.2 to 4.8)	5.0 (4.6 to 5.4)		0.021*
PSI class I-III	4.0 (3.6 to 4.4)	5.0 (4.5 to 5.5)		0.054*
PSI class IV-V	5.5 (4.4 to 6.6)	6.5 (5.5 to 7.5)		0.16*
Secondary ICU admission				
All patients	4 (2)	12 (7)	RR 0.31 (0.10 to 0.93)	0.027‡
PSI class I-III	0 (0)	6 (6)	-	0.009‡
PSI class IV-V	4 (6)	6 (9)	RR 0.65 (0.19 to 2.18)	0.48‡
30-day mortality				
All patients	3 (2)	7(4)	RR 0.40 (0.10 to 1.50)	0.16‡
PSI class I-III	0(0)	2 (2)	-	0.13‡
PSI class IV-V	3 (5)	5 (8)	RR 0.58 (0.14 to 2.33)	0.44‡

Data are median (95% CI) or number (%). ICU = Intensive care unit. PSI = Pneumonia Severity Index. RR = Risk ratio. *Gehan-Breslow-Wilcoxon test. ‡Chi-squared test. Numbers analysed: PSI I-III placebo (n= 102) and dexamethasone (n=114). PSI IV-V: placebo (n= 64) and dexamethasone (n=66).

Supplementary Table E4 Overview primary and secondary endpoints for subgroup analyses

Endpoint	Dexamethasone	Placebo	risk ratio (95% CI)	p-value
Length of stay (days)				
Initial CRP at admission				
CRP < 210 mg/l	4.5 (4.0 to 5.0)	5.0 (4.6 to 5.4)		0.28*
CRP ≥ 210 mg/l	5.0 (4.4 to 5.6)	5.5 (4.9 to 6.1)		0.046*
Pneumococcal urinary antigen test result				
Positive	5.0 (3.9 to 6.1)	6.0 (5.2 to 6.8)		0.45*
Negative	4.5 (4.1 to 4.9)	5.0 (4.5 to 5.5)		0.034*
Secondary ICU admission				
Initial CRP at admission				
CRP < 210 mg/l	3 (3)	6 (6)	RR 0.54 (0.14 to 2.11)	0.37‡
CRP ≥ 210 mg/l	2 (2)	8 (9)	RR 0.22 (0.05 to 1.01)	0.031‡
Pneumococcal urinary antigen test result				
Positive	0 (0)	0 (0)	-	-
Negative	4 (3)	11 (7)	RR 0.38 (0.12 to 1.17)	0.078‡
30-day mortality				
Initial CRP at admission				
CRP < 210 mg/l	3 (3)	5 (5)	RR 0.65 (0.16 to 2.65)	0.54‡
CRP ≥ 210 mg/l	1 (1)	2 (2)	RR 0.44 (0.04 to 4.77)	0.49‡
Pneumococcal urinary antigen test result				
Positive	0 (0)	1 (4)	-	0.26‡
Negative	4 (3)	5 (3)	RR 0.84 (0.23 to 3.06)	0.79‡

Data are median (95% CI) or number (%). ICU = Intensive care unit. RR = Risk ratio. CRP = C-reactive protein. Numbers analysed (dexamethasone/placebo): CRP < 210 mg/l (96/104), CRP ≥ 210 mg/l (107/94), Positive pneumococcal urinary antigen test result (32/26), negative pneumococcal urinary antigen test result (154/161). *Grehan-Breslow-Wilcoxon test. ‡Chi-squared test.

Supplementary Table E5 Reasons for ICU admission.

Patients	Age	PSI class	Reason for ICU admission
Placebo			
1	42	3	Respiratory failure
2	82	4	Respiratory failure
3	75	3	Respiratory failure
4	81	4	Respiratory failure
5	67	3	Observation after VATS[1] for empyema
6	85	3	Respiratory failure
7	69	2	Observation after VATS for empyema
8	66	3	Respiratory failure
9	59	4	Respiratory failure

Supplementary Table E5 Continued

Patients	Age	PSI class	Reason for ICU admission
10	58	4	Respiratory failure
11	85	4	Sepsis; Hypotension
12	65	4	Respiratory failure
13	56	4	Respiratory failure
14	80	5	Sepsis; Hypotension
Dexamethasone			
1	76	4	Respiratory failure
2	52	4	Respiratory failure
3	85	5	Arrhythmia with hypotension
4	85	4	Respiratory failure
5	80	4	Respiratory failure and pulmonary hemorrhage

[1]Video assisted thoracic surgery

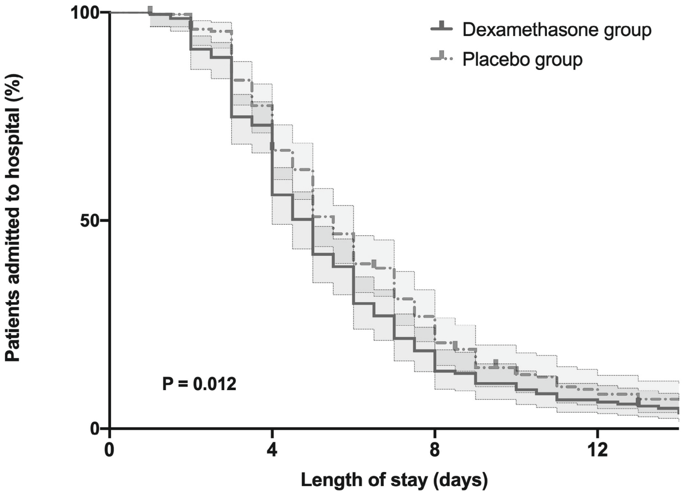
Supplementary Table E6 Cause of death

Patients	Age	PSI risk class	Cause of death
Placebo			
1	82	4	Respiratory failure; Severe legionella pneumonia
2	75	3	Respiratory failure; post-obstruction pneumonia newly diagnosed lung tumor
3	67	3	Died after VATS[1] for empyema
4*	58	4	Sepsis; Respiratory failure
5	85	4	Sepsis
6	77	4	Respiratory failure due to influenza pneumonia and congestive heart failure
7	84	4	Respiratory failure after opting for palliative care
8	81	4	Died 3 days after discharge; unknown cause of death
Dexamethasone			
1*	76	4	Died after ICU discharge due to multiple complications
2	80	4	Respiratory failure; Pulmonary hemorrhage
3	79	3	Strangulated femoral hernia after readmission
4	82	4	Respiratory failure; pulmonary infection and congestive heart failure
5	94	5	Died 10 days after discharge; unknown cause of death

*Died in hospital after 30 days of hospital admission. [1]Video assisted thoracic surgery.

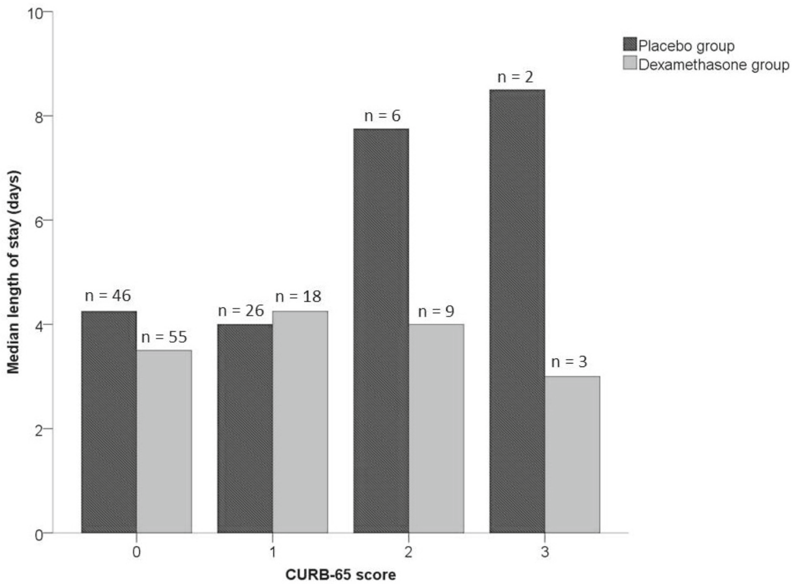
Supplementary Table E7 Reasons for readmission < 30 days of admission

Patients	Age	PSI risk class	Reason for readmission
Placebo			
1	52	3	Antrum gastritis
2	70	3	Mediastinitis
3	44	1	Hospital-acquired pneumonia; urticarial reaction to amoxicillin/clavulanic acid
4	90	4	Urosepsis
5	54	3	Relapse of pulmonary infection
6	71	4	Psychiatric complaints
7	40	1	Bronchiolitis
8	67	3	Relapse of pulmonary infection
9	71	5	Relapse of pulmonary infection
Dexamethasone			
1	79	3	Strangulated femoral hernia
2	82	4	Relapse of pulmonary infection and congestive heart failure
3	69	5	Congestive heart failure
4	74	3	Relapse of pulmonary infection
5	56	2	Altered mental status
6	84	4	Hospital-acquired pneumonia
7	61	2	Angina Pectoris
8	46	1	Relapse of pulmonary infection
9	76	4	Relapse of pulmonary infection
10	61	2	Elective cardioversion for atrial fibrillation
11	85	5	Fever of unknown origin
12	54	2	Urine retention
13	56	2	Relapse of pulmonary infection
14	61	3	Chest pain caused by pleurisy
15	61	5	Ischemic cerebrovascular accident
16	84	4	Fatigue
17	27	1	Relapse of pulmonary infection
18	71	4	Dehydration and altered mental status
19	64	4	Relapse of pulmonary infection
20	85	4	Acute decompensated heart failure



Number at risk				
Dexamethasone group	203	148	38	14
Placebo group	198	152	51	16

Supplementary Figure E1 Kaplan-Meier analysis of the effect of dexamethasone on length of hospital stay in all enrolled patients including ICU patients



Supplementary Figure E2 Length of stay according to CURB-65 score and treatment group in patients under 65 years of age