Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response
A Randomized Clinical Trial

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IMPORTANCE In patients with severe community-acquired pneumonia, treatment failure is associated with excessive inflammatory response and worse outcomes. Corticosteroids may modulate cytokine release in these patients, but the benefit of this adjunctive therapy remains controversial.

OBJECTIVE To assess the effect of corticosteroids in patients with severe community-acquired pneumonia and high associated inflammatory response.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled trial conducted in 3 Spanish teaching hospitals involving patients with both severe community-acquired pneumonia and a high inflammatory response, which was defined as a level of C-reactive protein greater than 150 mg/L at admission. Patients were recruited and followed up from June 2004 through February 2012.

INTERVENTIONS Patients were randomized to receive either an intravenous bolus of 0.5 mg/kg per 12 hours of methylprednisolone (n = 61) or placebo (n = 59) for 5 days started within 36 hours of hospital admission.

MAIN OUTCOMES AND MEASURES The primary outcome was treatment failure (composite outcome of early treatment failure defined as [1] clinical deterioration indicated by development of shock, [2] need for invasive mechanical ventilation not present at baseline, or [3] death within 72 hours of treatment; or composite outcome of late treatment failure defined as [1] radiographic progression, [2] persistence of severe respiratory failure, [3] development of shock, [4] need for invasive mechanical ventilation not present at baseline, or [5] death between 72 hours and 120 hours after treatment initiation; or both early and late treatment failure). In-hospital mortality was a secondary outcome and adverse events were assessed.

RESULTS There was less treatment failure among patients from the methylprednisolone group (8 patients [13%]) compared with the placebo group (18 patients [31%]) (P = .02), with a difference between groups of 18% (95% CI, 3% to 32%). Corticosteroid treatment reduced the risk of treatment failure (odds ratio, 0.34 [95% CI, 0.14 to 0.87]; P = .02). In-hospital mortality did not differ between the 2 groups (6 patients [10%] in the methylprednisolone group vs 9 patients [15%] in the placebo group; P = .37); the difference between groups was 5% (95% CI, −6% to 17%). Hyperglycemia occurred in 11 patients (18%) in the methylprednisolone group and in 7 patients (12%) in the placebo group (P = .34).

CONCLUSIONS AND RELEVANCE Among patients with severe community-acquired pneumonia and high initial inflammatory response, the acute use of methylprednisolone compared with placebo decreased treatment failure. If replicated, these findings would support the use of corticosteroids as adjunctive treatment in this clinical population.

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Community-acquired pneumonia is the leading infectious cause of death in developed countries. Despite advances in antibiotic treatment, mortality among hospitalized patients with community-acquired pneumonia is still high, especially in those with severe pneumonia[1,2] and in those who experience treatment failure[3,4] (observed in 10%-20% of patients). In an earlier study conducted by the Neumofail Group,[3] patients with treatment failure had higher mortality compared with those who did not experience treatment failure (25% vs 2%, respectively), and it was possible to use treatment failure as a surrogate parameter for mortality. In patients with community-acquired pneumonia, an excessive host inflammatory response is associated with treatment failure during intensive care unit (ICU) admission[5] and mortality.[6]

Corticosteroids inhibit the expression and action of many cytokines involved in the inflammatory response associated with pneumonia.[7] In clinical practice, use of corticosteroids for patients with community-acquired pneumonia remains controversial, with some studies showing a benefit in clinical outcomes (radiographic progression, prevention of shock, respiratory failure, length of stay, and mortality),[8-11] and another study showing no effect.[12]

However, most of these studies[10,11,13] did not include patients with the most severe cases of community-acquired pneumonia and all of them enrolled patients without consideration of the level of initial systemic inflammatory response. Two meta-analyses[14,15] found improved mortality in the subgroup of patients with severe community-acquired pneumonia who received corticosteroid treatment.

Our hypothesis was that corticosteroids may modulate cytokine release in these patients. Reducing inflammation may be followed by a decrease in treatment failure in hospitalized patients with community-acquired pneumonia. By examining treatment failure in a placebo-controlled intervention limited to only patients with severe community-acquired pneumonia and a high inflammatory response, we targeted those most likely to benefit (and least likely to be harmed due to superinfection) from corticosteroids.

Methods

Design and Patients

We undertook a multicenter, randomized, double-blind, placebo-controlled trial in patients with severe community-acquired pneumonia and a high inflammatory response at 3 Spanish teaching hospitals. Patients were prospectively enrolled and followed up from June 2004 through February 2012. Additional details about the trial protocol appear in Supplement 1 and in the eMethods in Supplement 2. The local ethics committees approved the study protocol and written informed consent was obtained from all participants or their authorized representatives.

Patients were eligible if they met the following criteria: (1) were aged 18 years or older, (2) had clinical symptoms suggesting community-acquired pneumonia (cough, fever, pleuritic chest pain, or dyspnea), (3) had a new chest radiographic infiltrate, (4) met severe community-acquired pneumonia criteria (defined by modified American Thoracic Society criteria[16] or risk class V for the Pneumonia Severity Index[17]), and (5) had a C-reactive protein (CRP) level of greater than 150 mg/L at admission (to convert CRP to mmol/L, multiply by 9.524). The rationale for this cutoff comes from the analyses performed in the study by the Neumofail Group,[3] which included some of us. A CRP level of 150 mg/L was the 25th percentile of patients with community-acquired pneumonia and treatment failure, and we expected that choosing the 25th percentile would increase the chance of recruiting patients with a high inflammatory response. We published these data in 2008.[18]

Patients were excluded if they had 1 of the following criteria: (1) prior treatment with systemic corticosteroids, (2) nosocomial pneumonia, (3) reported severe immunosuppression (human immunodeficiency virus infection, immunosuppressive conditions or medications), (4) preexisting medical condition with a life expectancy of less than 3 months, (5) uncontrolled diabetes mellitus, (6) major gastrointestinal bleeding within 3 months, or (7) a condition requiring acute treatment with greater than 1 mg/kg/d of methylprednisolone or its equivalent. Patients with pandemic H1N1 influenza A pneumonia were excluded.

Procedures

Patients were randomized to receive either an intravenous bolus of 0.5 mg/kg per 12 hours of methylprednisolone or placebo for 5 days started within 36 hours of hospital admission. Randomization was based on 1-to-1 allocation of prenumbered boxes containing dosing units with identical appearance for methylprednisolone and placebo. Patients, investigators, and data assessors were blinded to treatment allocation.

All patients were treated with antibiotics according to international guidelines.[19] Antibiotic treatments were not guided by levels of procalcitonin.

Definitions

The primary efficacy outcome was the rate of treatment failure, which includes treatment failure that occurred early, late, or at both times. Early treatment failure was defined as clinical deterioration within 72 hours of treatment (included development of shock, need for invasive mechanical ventilation not present at baseline, or death). Late treatment failure was defined as radiographic progression (increase of ≥50% of pulmonary infiltrates compared with baseline), persistence of severe respiratory failure (ratio of Pa_{O_2} to fraction of inspired oxygen <200 mm Hg, with respiratory rate ≥30 breaths/min in patients not intubated), development of shock, need for invasive mechanical ventilation not present at baseline, or death between 72 hours and 120 hours after treatment initiation. These criteria have been used previously with modifications.[3]

Secondary efficacy outcomes included time to clinical stability, length of ICU and hospital stays, and in-hospital mortality. Clinical stability was modified from the definition by Halm et al,[20] and was determined when the following values were achieved for all parameters: temperature of 37.2°C or lower, heart rate of 100 beats/min or lower, systolic blood pres-

sure of 90 mm Hg or higher, and arterial oxygen tension of 60 mm Hg or higher when the patient was not receiving supplemental oxygen. In patients receiving oxygen therapy at home, stability was considered to be achieved when their oxygen needs were the same as before admission. Oral switch was defined when intravenous antibiotics for patients with community-acquired pneumonia were stopped and the same class of them were administered orally.

Microbiological examination was performed at the time of clinical presentation and included collection of a sputum sample, urine sample, 2 samples of blood, and nasopharyngeal swab samples. Thoracocentesis and bronchoscopic samples were obtained when possible. The criteria for microbiological diagnosis were described elsewhere.[21]

Standard laboratory assessment performed at presentation included renal and liver functions, electrolytes, blood glucose, CRP, and hematology. Arterial blood gases were performed at admission and thereafter as clinically indicated.

Interleukin 6, IL-8, IL-10, procalcitonin, and CRP levels were obtained on the first day and after 3 days and 7 days of treatment. The laboratory techniques used were described elsewhere.[5]

Adverse events during hospital stay included hyperglycemia, superinfection, gastrointestinal bleeding, delirium, acute kidney injury, and acute hepatic failure. Superinfection was considered to have occurred when patients tested positive for a nosocomial infection of any source.

Statistical Analysis

The study was based on the assumption that the placebo group would have a treatment failure rate of 35%.[3] According to a 2-sided type I error of 0.05 and 80% power to detect an absolute 20% reduction in treatment failure by methylprednisolone compared with placebo, the sample size was 60 patients in each group. The rationale comes from the study by the Neumofail Group,[3] which included some of us and was a prospective, multicenter, observational study designed to evaluate the rates of treatment failure in a general population of patients with community-acquired pneumonia. In that study, we found a total treatment failure rate of 15% and a mortality rate of 25% in patients with treatment failure; however, only 2% of the study population did not experience treatment failure. Even though mortality was not the primary study outcome, we thought that a 20% rate of treatment failure was clinically relevant because this could have an important effect on other outcomes such as the need for mechanical ventilation and length of ICU and hospital stay.

A prespecified interim analysis was planned at 50% (60 of 120) of patient accrual. In the primary efficacy outcome comparison, a P value of less than .03 was considered to indicate significance to maintain an overall type I error of 0.05 for the interim and final analyses (Pocock test). The interim analysis showed no significant differences with regard to treatment failure (3 of 30 patients [10%] in the methylprednisolone group vs 9 of 30 patients [30%] in the placebo group, P = .05); therefore, the study was continued as planned.

Efficacy data were analyzed for both the intention-to-treat and the per-protocol populations. The intention-to-treat population included all randomized patients who received at least 1 dose of the study drug. The per-protocol population included all randomized patients who met all inclusion criteria, received at least 6 doses of the study drug, and did not have serious deviations from the protocol.

We report the number and percentage of patients for categorical variables, the median and interquartile range for continuous variables with nonnormal distribution, and the mean and standard deviation for those with normal distribution. Categorical variables were compared using the χ^2 test or the Fisher exact test. Continuous variables were compared using the t test or the nonparametric Mann-Whitney test. We calculated 95% confidence intervals for differences in outcome rates and medians. As sensitivity analyses, we performed logistic regression models to examine differences in the primary outcome between the 2 groups, as well as in early and late treatment failure and the single components, to provide supportive information.

We assessed differences in time to treatment failure between groups using the Kaplan-Meier method (log-rank test). Differences in secondary outcomes (time to clinical stability and length of ICU and hospital stay) between both treatment groups were also analyzed with Cox proportional hazard regression models. In-hospital mortality was analyzed using logistic regression models. The primary and secondary outcomes were analyzed both without an adjustment for baseline variables and with adjustment for potential confounders, including 2 predefined covariates (ie, the year of admission and the center) and all the variables for which there was an imbalance between the 2 groups at baseline (P < .10).

The goodness of fit of the models was tested using the Hosmer-Lemeshow test or deviance residuals. Proportional hazards assumptions were tested with log minus log plots. We performed post hoc subanalyses according to treatment failure and late treatment failure that did not include the radiographic progression.

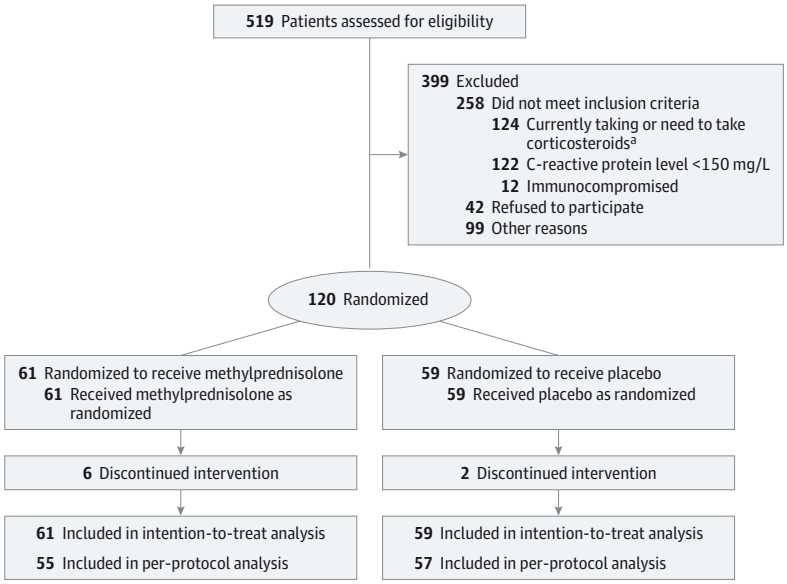
All tests were 2-tailed and significance was set at .05. All analyses were performed with SPSS Statistics version 20.0 (SPSS Inc).

Results

Of 519 patients screened, 120 patients were randomized, and 112 (93%) completed the study (**Figure 1**). The data are reported on an intention-to-treat basis unless otherwise indicated. The differences in baseline characteristics between patients enrolled in 2004-2007 and those enrolled in 2008-2012 are summarized in eTable 1 in Supplement 2.

Baseline characteristics comparing patients who received methylprednisolone with those who received placebo appear in **Table 1**. Both groups had similar baseline characteristics, except for lower levels of procalcitonin and IL-10 at day 1, and lower proportions of patients with septic shock in the methylprednisolone group (Table 1). Ninety patients (75%) were admitted to the ICU at the time of enrollment. Patients admitted to the ward initially and then transferred to the ICU are summarized in Table 1 and eTable 2 in Supplement 2. We did not find differences in time to first

Figure 1. Flow Diagram of the Study With Detailed Information on Allocation and the Excluded Patients



[a] Indicates those who were treated with corticosteroids for any other reason.

dose of antibiotics (both in patients with and without shock) in those initially admitted to the ward and transferred to the ICU, from emergency department arrival, and randomization (eTable 3 in Supplement 2).

The rate of etiologic diagnosis was higher in the methylprednisolone group (eTable 4 in Supplement 2). *Streptococcus pneumoniae* was the most common etiologic agent in both groups. Distribution of the pathogens did not differ between groups.

Antimicrobial treatment was similar in both study groups (eTable 5 in Supplement 2). Combinations of ceftriaxone with levofloxacin and with azithromycin were the most common antibiotics used at admission. There were no differences in the percentage of patients treated with a macrolide plus another antibiotic. Among the 49 patients with a positive microbiologic diagnosis, the initial empirical treatment was changed in 15 cases after these results were obtained (in 6 cases for treatment adjustment [ie, narrowing the antimicrobial spectrum], in 5 cases due to treatment failure, and in 4 cases for oral switch).

The initial adequacy of antibiotic treatment was similar (97% in each group according to guidelines and according to microbiological results). There were 49 cases with microbial etiology (excluding the 6 cases with only viruses detected). In the remaining 43 patients, initial antibiotic adequacy was 94% in the placebo group (16/17 patients) and 100% in the treatment group (26 patients). The time to first antibiotic dose and the duration of antibiotic treatment did not differ between groups either.

There was less treatment failure in the methylprednisolone group (8 patients [13%]) compared with the placebo group (18 patients [31%]) (P = .02). The difference between groups was 18% (95% CI, 3%-32%) due to fewer cases of late treatment failure and radiographic progression (**Table 2**). Similar results were obtained in the per-protocol population.

Post hoc subanalyses showed a significant difference in late treatment failure that did not include the radiographic progression in favor of the methylprednisolone group (8 patients [14%] vs 2 patients [3%] in the placebo group; P = .04) in the intention-to-treat population (difference between groups, 10% [95% CI, 0%-20%]). There was not a significant difference in the per-protocol population in favor of the methylprednisolone group (8 patients [14%] vs 2 patients [4%] in the placebo group; P = .05; difference between groups, 10% [95% CI, 0%-21%]).

Logistic regression analyses revealed that methylprednisolone reduced the risk of treatment failure, both without adjustment for baseline variables and with adjustment for septic shock, procalcitonin, and IL-10 at day 1, year of admission, and center (**Table 3**). Similar results were obtained in the per-protocol population. Late treatment failure also reflected a protective effect with corticosteroids both in the intention-to-treat and the per-protocol populations. Time to treatment failure differed significantly between groups in the Kaplan-Meier analysis (**Figure 2**). In eFigure 1 in Supplement 2, the proportions of patients with septic shock and the need for mechanical ventilation (early and late treatment failure combined) did not differ between groups, whereas patients included in the methylprednisolone group had less radiographic progression compared with the placebo group. Similar results were obtained in the per-protocol population.

No statistically significant differences were observed among secondary clinical outcomes (Table 2 and Table 3). In-hospital mortality did not differ between groups (6 patients [10%] in the methylprednisolone group vs 9 patients [15%] in the placebo group; P = .37; difference between groups, 5% [95% CI, −6% to 17%]), even after adjustment for potential confounders. Similar results were obtained in the per-protocol

Table 1. Baseline Characteristics of the Intention-to-Treat Population

	Methylprednisolone (n = 61)	Placebo (n = 59)
Age, mean (SD), y	64.5 (19.1)	66.1 (20.1)
Male sex, No. (%)	35 (57)	39 (66)
Current smoker, No. (%)	15 (25)	17 (29)
Preexisting comorbid conditions, No. (%)[a]		
Diabetes mellitus	10 (16)	13 (22)
Chronic pulmonary disease	7 (11)	12 (20)
Congestive heart failure	22 (36)	24 (41)
History of malignancy	3 (5)	8 (14)
Ischemic heart disease	12 (20)	9 (15)
Symptoms, No. (%)		
Fever	48 (79)	41 (69)
Altered mental status	13 (21)	14 (24)
Breathlessness	35 (57)	36 (61)
Cough	46 (75)	40 (68)
Chills	23 (38)	20 (34)
Chest pain	21 (34)	26 (44)
Clinical signs, mean (SD)		
Temperature, °C	37.6 (1.1)	37.6 (1.0)
Respiratory rate, breaths/min	30.0 (8.0)	29.7 (8.9)
Heart rate, beats/min	105.5 (20.6)	113.5 (23.7)
Serum levels, median (IQR)		
Glucose, mg/dL	131 (106-159)	129 (107-180)
Creatinine, mg/dL	1.3 (0.9-1.8)	1.3 (1.0-1.8)
Platelets, $\times 10^9$/L	214 (176-282)	217 (175-283)
White blood cell count, $\times 10^9$/L	12.7 (9.0-17.2)	14.4 (9.2-23.0)
C-reactive protein, mg/L[b]	273 (202-292)	244 (172-289)
Procalcitonin, ng/dL[b]	1.3 (0.4-4.4)	3.1 (0.8-9.5)
IL-6, pg/dL[b]	256 (133-674)	316 (182-834)
IL-8, pg/dL[b]	74 (34-107)	88 (55-182)
IL-10, pg/dL[b]	4.7 (2.8-9.2)	8.1 (4.0-13.5)
Ratio of IL-6 to IL-10[b]	0.02 (0.01-0.03)	0.02 (0.01-0.04)
Ratio of Pao_2 to fraction of inspired oxygen, mean (SD), mm Hg	236 (75)	230 (83)
Pleural effusion, No. (%)	11 (18)	12 (20)
Pneumonia Severity Index score, mean (SD)[17]	107 (38)	110 (35)
Risk class, No. (%)[c]		
I-III	18 (30)	14 (24)
IV	21 (34)	26 (44)
V	22 (36)	19 (32)
Major severity criteria,[16] No. (%)[d]		
Mechanical ventilation	5 (8)	10 (17)
Noninvasive alone	3 (5)	5 (8)
Noninvasive followed by invasive	1 (2)	3 (5)
Invasive alone	1 (2)	2 (3)
Septic shock	10 (17)	18 (31)
Minor severity criteria, No. (%)[16]		
Systolic blood pressure <90 mm Hg	11 (18)	17 (29)
Multilobar involvement	37 (61)	34 (58)
Ratio of Pao_2 to fraction of inspired oxygen <250 mm Hg, No. (%)	42 (70)	40 (68)
ICU admission, No. (%)	43 (70)	47 (80)
Time to first antibiotic dose, No. (%)		
Within 1 h in patients with septic shock[e]	3 (30)	5 (28)
Within 4 h in patients without septic shock[f]	35 (74)	27 (71)
Macrolide combination therapy, No. (%)	15 (24)	13 (23)
Time from emergency department presentation to randomization, median (IQR), d	1 (0-1)	0 (0-1)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

SI conversion factors: To convert C-reactive protein to mmol/L, multiply by 9.524; creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555.

[a] Could have more than 1 comorbid condition.

[b] Calculated at day 1.

[c] Stratified according to 30-day risk mortality for community-acquired pneumonia: risk classes I-III (≤90 points) have low mortality (range, 0%-10%) and risk class IV (91-130 points) and risk class V (>130 points) have the highest mortality (range, 10%-35%).

[d] Two patients (3%) in the methylprednisolone group and 4 patients (7%) in the placebo group had both septic shock and the need for mechanical ventilation.

[e] Ten patients in the methylprednisolone group and 18 patients in the placebo group were used to calculate the percentages.

[f] Forty-seven patients in the methylprednisolone group and 38 patients in the placebo group were used to calculate the percentages.

Table 2. Clinical Outcomes Using Descriptive Statistics for the Intention-to-Treat and Per-Protocol Populations

	Intention-to-Treat Population				Per-Protocol Population			
	Methylprednisolone Group (n = 61)	Placebo Group, (n = 59)	*P* Value	Difference Between Groups, % (95% CI)	Methylprednisolone Group (n = 55)	Placebo Group (n = 57)	*P* Value	Difference Between Groups, % (95% CI)
Primary Clinical Outcome								
Treatment failure, No. (%)[a]	8 (13)	18 (31)	.02	18 (3 to 32)	5 (9)	16 (28)	.01	19 (5 to 33)
Early treatment failure (0-72 h), No. (%)[b]	6 (10)	6 (10)	.95	0 (−10 to 11)	3 (5)	4 (7)	>.99	2 (−7 to 11)
Early mechanical ventilation	4 (7)	5 (8)	.74	2 (−8 to 11)	2 (4)	3 (5)	>.99	2 (−6 to 9)
Early septic shock	2 (3)	3 (5)	.68	2 (−5 to 9)	1 (2)	2 (4)	>.99	2 (−4 to 8)
Death	2 (3)	2 (3)	>.99	0 (−6 to 7)	0	0		
Late treatment failure (72-120 h), No. (%)[b]	2 (3)	15 (25)	.001	22 (10 to 34)	2 (4)	14 (25)	.002	21 (9 to 33)
Radiographic progression	1 (2)	9 (15)	.007	14 (4 to 23)	1 (2)	8 (14)	.03	12 (3 to 22)
Respiratory failure	1 (2)	5 (8)	.11	7 (−1 to 15)	1 (2)	5 (9)	.21	7 (−1 to 15)
Late mechanical ventilation	1 (2)	4 (7)	.20	5 (−2 to 12)	1 (2)	4 (7)	.36	5 (−2 to 13)
Late septic shock	0	4 (7)	.06	7 (0 to 13)	0	4 (7)	.12	7 (0 to 14)
Death	0	0			0	0		
Secondary Clinical Outcomes								
Time to clinical stability, median (IQR), d[c]	4 (3 to 6)	5 (3 to 7)	.28	1 (−0.4 to 2.4)	4 (3 to 6)	5 (3 to 7)	.13	1 (0 to 2)
Length of stay, median (IQR), d								
Hospital	11 (7.5 to 14)	10.5 (8 to 15)	.83	−0.5 (−4.6 to 3.6)	11 (8 to 14)	11.5 (8 to 15)	.70	0.5 (−3.3 to 4.3)
ICU[d]	5 (3 to 8)	6 (4 to 8)	.63	1 (−0.4 to 2.4)	5 (3 to 8)	6 (4 to 8)	.38	1 (0 to 2)
In-hospital mortality, No. (%)	6 (10)	9 (15)	.37	5 (−6 to 17)	3 (5)	7 (12)	.21	7 (−4 to 17)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Defined as the presence of early or late failure or both.

[b] Several patients had more than 1 criteria of failure.

[c] Clinical stability was considered to be attained when the following values were achieved for all parameters: temperature of 37.2°C or lower; heart rate of 100 beats/min or lower; systolic blood pressure of 90 mm Hg or higher; and arterial oxygen tension of 60 mm Hg or higher when the patient was not receiving supplemental oxygen. In patients who were receiving home oxygen therapy, stability was considered to be achieved when their oxygen needs were the same as before admission.

[d] There were 42 patients in the methylprednisolone group and 46 patients in the placebo group in the intention-to-treat population and 37 patients in the methylprednisolone group and 44 patients in the placebo group in the per-protocol population.

population. Causes of death were similar between the 2 groups (eTable 6 in Supplement 2).

Changes from day 1 in CRP, procalcitonin, IL-6, IL-8, and IL-10 at days 3 and 7 are shown in eFigure 2 in Supplement 2. At day 3, the decrease in levels of CRP and IL-10 were higher in the methylprednisolone group. At day 7, the decrease in levels of CRP remained higher in the methylprednisolone group. We did not observe a rebound of inflammation 2 days (day 7) after stopping methylprednisolone. However, we did not collect blood samples after day 7 and cannot comment on the cytokine levels after day 7. The hospital outcomes of patients with a still high level of CRP at day 7 compared with those in whom it was decreased at the same time are summarized in eTable 7 in Supplement 2. Patients with a persistently high inflammatory response at day 7 had a higher percentage of treatment failure and mortality.

Adverse events were evenly distributed across the 2 groups (eTable 8 in Supplement 2). Hyperglycemia occurred in 11 patients (18%) in the methylprednisolone group and in 7 patients (12%) in the placebo group ($P = .34$). Acute kidney injury occurred in 8 patients (13%) in the methylprednisolone group and in 8 patients (14%) in the placebo group ($P = .85$). One patient in the methylprednisolone group had a superinfection. Another patient in the methylprednisolone group had delirium. Another patient in the methylprednisolone group developed an acute hepatic failure. One patient in the placebo group had gastrointestinal bleeding.

Discussion

The results demonstrated that the acute administration of methylprednisolone was associated with less treatment failure and a lower inflammatory response in a prospectively identified population of patients with both severe community-acquired pneumonia and a high inflammatory response (defined as a CRP level >150 mg/L at admission).

Severe community-acquired pneumonia remains a major cause of mortality, and despite effective antibiotic therapy, 12% to 36% of patients admitted to the ICU die within a short period.[2,22,23] In addition, patients in risk class V for the Pneumonia Severity Index also have a high mortality risk.[24] Therefore, the development of an efficacious adjunctive treatment has important implications for reducing this high rate of mortality.

Table 3. Clinical Outcomes for the Methylprednisolone Group vs Placebo Group Using Logistic Regression or Cox Proportional Hazards Models for the Intention-to-Treat and Per-Protocol Populations

	Intention-to-Treat Population				Per-Protocol Population			
	Unadjusted OR or HR (95% CI)	*P* Value	Adjusted OR or HR (95% CI)[a]	*P* Value	Unadjusted OR or HR (95% CI)	*P* Value	Adjusted OR or HR (95% CI)[a]	*P* Value
Primary Clinical Outcome								
Treatment failure[b]	0.34 (0.14-0.87)	.02	0.33 (0.12-0.90)	.03	0.26 (0.09-0.76)	.01	0.26 (0.08-0.79)	.02
Early treatment failure (0-72 h)[c]	0.96 (0.29-3.18)	.95	1.14 (0.28-4.67)	.86	0.76 (0.16-3.58)	.73	0.93 (0.17-5.06)	.94
Early mechanical ventilation	0.76 (0.19-2.97)	.69	1.02 (0.18-5.83)	.98	0.68 (0.11-4.23)	.68	0.77 (0.09-6.46)	.81
Early septic shock	0.63 (0.10-3.93)	.62	0.38 (0.03-4.42)	.44	0.51 (0.05-5.78)	.59	0.42 (0.04-4.90)	.49
Death	0.97 (0.13-7.09)	.97	1.35 (0.04-40.84)	.86				
Late treatment failure (72-120 h)[c]	0.10 (0.02-0.46)	.003	0.09 (0.02-0.47)	.004	0.12 (0.03-0.54)	.006	0.11 (0.02-0.52)	.006
Radiographic progression	0.09 (0.01-0.76)	.03	0.09 (0.01-0.78)	.03	0.11 (0.01-0.94)	.04	0.10 (0.01-0.84)	.03
Respiratory failure	0.18 (0.02-1.59)	.12	0.14 (0.01-1.35)	.09	0.19 (0.02-1.71)	.14	0.15 (0.02-1.50)	.11
Late mechanical ventilation	0.23 (0.03-2.11)	.19	0.20 (0.02-1.91)	.16	0.25 (0.03-2.27)	.22	0.22 (0.02-2.10)	.19
Late septic shock	0 (0-∞)[d]	>.99	0 (0-∞)[d]	>.99	0 (0-∞)[d]	>.99	0 (0-∞)[d]	>.99
Death	0		0		0		0	
Secondary Clinical Outcomes								
Time to clinical stability, d[e]	1.16 (0.78-1.73)	.46	1.11 (0.72-1.71)	.64	1.24 (0.83-1.87)	.29	1.20 (0.77-1.85)	.42
Length of stay, d								
Hospital	0.66 (0.23-1.85)	.43	0.61 (0.19-1.93)	.40	0.47 (0.12-1.81)	.27	0.40 (0.10-1.63)	.20
ICU[f]	0.18 (0.02-1.46)	.11	0.13 (0.01-1.44)	.10	0.02 (0-60.31)	.33	0 (0-∞)[d]	.29
In-hospital mortality	0.61 (0.20-1.82)	.37	0.57 (0.16-2.00)	.38	0.41 (0.10-1.68)	.22	0.38 (0.08-1.70)	.21

Abbreviation: HR, hazard ratio; ICU, intensive care unit; OR, odds ratio.

[a] Adjusted for septic shock, procalcitonin, and IL-10 at day 1, year of admission, and center.

[b] Defined as the presence of early or late failure or both.

[c] Several patients had more than 1 criteria of failure.

[d] Estimation failed due to numerical problem. Because the coefficients did not converge, no further models were fitted.

[e] Clinical stability was considered to be attained when the following values were achieved for all parameters: temperature of 37.2°C or lower; heart rate of 100 beats/min or lower; systolic blood pressure of 90 mm Hg or higher; and arterial oxygen tension of 60 mm Hg or higher when the patient was not receiving supplemental oxygen. In patients who were receiving home oxygen therapy, stability was considered to be achieved when their oxygen needs were the same as before admission.

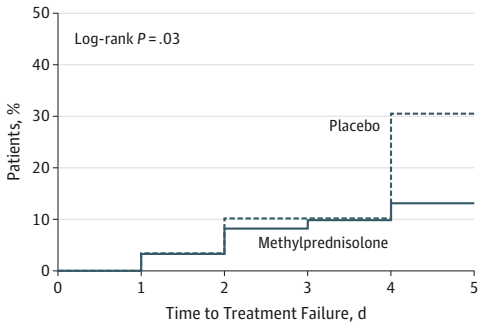
[f] There were 42 patients in the methylprednisolone group and 46 patients in the placebo group in the intention-to-treat population and 37 patients in the methylprednisolone group and 44 patients in the placebo group in the per-protocol population.

A key factor determining the evolution of severe community-acquired pneumonia is the host response. Studies on severe pneumonia have shown an increase in serum levels for cytokines such as IL-6, IL-8, and IL-10.[25-27] A recent study showed that excess serum levels for IL-6 and IL-10 were associated with a high mortality rate among patients with community-acquired pneumonia.[28]

Corticosteroids are the most effective and widely used anti-inflammatory drugs. Experimental studies have shown that acute administration of corticosteroids reduces inflammatory cytokines in patients with severe pneumonia.[29,30] Moreover, we previously demonstrated that use of methylprednisolone and antibiotics in a piglet model of severe pneumonia also decreased bacterial burden better than antibiotics alone.[29] Therefore, we limited our intervention to patients with both severe community-acquired pneumonia and a high initial systemic inflammatory response only.

The rate of treatment failure in the control group was 31%, which is consistent with a previous study[3] that reported a treatment failure rate of 35% in patients with severe community-acquired pneumonia. Treatment failure was reduced from 31% to 13% in patients treated with methylprednisolone. Treatment failure can occur either early or late,[3,18] and we observed a reduction in late treatment failure with steroid therapy, primarily due to a decrease in radiographic progression and the late appearance of septic shock. These 2 variables have been

Figure 2. Kaplan-Meier Analysis of the Effect of Methylprednisolone on Time to Treatment Failure



No. at risk

Placebo	59	57	53	53	41	41
Methylprednisolone	61	59	56	55	53	53

associated with higher mortality in patients with severe community-acquired pneumonia.[31,32]

The main benefit of our study was the decrease in radiographic progression (>50% progression in the pulmonary infiltrates). This variable has been found as an independent surrogate marker of mortality in previous studies of community-acquired pneumonia.[33] We performed post hoc analyses excluding radiographic progression and the statistical differences for lower rates of treatment failure remained in favor of the methylprednisolone group. This indicates that even with excluding radiographic progression (the dominant individual component of treatment failure), the beneficial effects of corticosteroids remained.

After adjusting for potential confounders such as septic shock, levels of procalcitonin and IL-10 at day 1, year of admission, and center, methylprednisolone use reduced the risk of late treatment failure, particularly for radiographic progression. Confalonieri et al[8] also reported an improvement in chest radiograph score in patients with severe community-acquired pneumonia treated with corticosteroids. No other recent randomized control trials have evaluated treatment failure in patients with severe community-acquired pneumonia receiving corticosteroids as adjunctive therapy.[8,10,11] Nevertheless, Nie et al[14] performed a meta-analysis including all randomized control trials that used corticosteroids in populations with community-acquired pneumonia from 1956 to 2011. Even though treatment failure was not evaluated, Nie et al[14] showed that the use of corticosteroids was associated with improved survival in patients with severe community-acquired pneumonia.

In another meta-analysis that included trials with severe and nonsevere community-acquired pneumonia, Confalonieri et al[15] observed a decrease in mortality in favor of steroids in the population with severe community-acquired pneumonia. We found no differences in mortality when comparing both study groups. However, the sample size was chosen based on treatment failure rather than in-hospital mortality. We speculate that having less treatment failures could lead to decreased mortality in community-acquired pneumonia, but if this outcome had been chosen, a larger study population would have been required.[3,4]

A systemic reduction in inflammatory biomarkers was observed during the study in both groups, with higher decreases in levels of CRP and IL-10 in patients receiving methylprednisolone. These findings are consistent with previous studies that have found those patients with community-acquired pneumonia treated with corticosteroids experienced a greater decline in levels of CRP[8,10,11,13] and IL-6.[10,11]

The effects of steroids on the immune system are many and complex. Corticosteroids can switch off genes that encode proinflammatory cytokines (eg, IL-6, IL-8) and switch on genes that encode anti-inflammatory cytokines (eg, IL-10).[7] However, the use of steroids also exerts an influence on the immune function of different host defenses against bacteria when high dosages and prolonged treatment are used,[7,34] which was not the case in our study. The Corticosteroid Therapy of Septic Shock study[33] reported more episodes of superinfection (including sepsis and septic shock) in patients treated with corticosteroids; however, when only superinfections were examined, the rates for both the treatment and placebo groups were similar.

In our study, the use of methylprednisolone was not associated with superinfection or other adverse events. Previous studies of community-acquired pneumonia did not find higher rates of superinfection or other potentially adverse events in patients treated with corticosteroids,[8,10,11,13] except for hyperglycemia.[11,14] In a subset analysis of a prospective randomized control trial, corticosteroid therapy for community-acquired pneumonia reduced mortality for those with a high inflammatory response and a low cortisol level.[35] These findings are consistent with the data in our study, although we did not measure cortisol levels. According to that study and others in the literature, the immunosuppression caused by corticosteroids was probably not relevant when administered acutely, in contrast to chronic treatment. In addition, high dosages are not the same as the relatively low dosages used in our study.

The duration of treatment with steroids in our trial was 5 days and was not followed by a gradual tapering. We obtained only 1 blood collection during the treatment intervention (day 3); we interpret the CRP data on day 7 to indicate a lack of rebound inflammation within 48 hours of stopping treatment. Others have reported rebound inflammation 72 hours after discontinuing corticosteroids without tapering.[11,36]

The main strength and the most important characteristic of our trial, differing from previous studies, was the inclusion of patients with severe community-acquired pneumonia and a high systemic inflammatory response. Thus, we selected the patients most likely to benefit from our intervention. Initial high levels of inflammation are associated with higher rates of treatment failure in patients with community-acquired pneumonia.[18] Thus, the results of this trial cannot be applied to patients with a CRP level lower than 150 mg/L.

In fact, 24% of screened patients were not included due to having CRP levels lower than this cutoff (Figure 1). In addition, using a novel clinical outcome such as treatment failure (mainly late treatment failure) may assist future studies in understanding the benefits of this therapy without including a large population that would be needed if mortality was the outcome chosen.[37] The beneficial effects found in our study with regard to treatment failure (mainly radiographic progression) fit with previous trials in the literature; one was stopped prematurely[8] and another was very small.[10]

Our study has limitations. First, the results cannot be generalized to all patients with community-acquired pneumonia. Second, no assessment of adrenal function was performed and it is possible that administration of methylprednisolone may have helped patients with relative adrenal insufficiency and may have been less valuable in those without adrenal insufficiency, as recently suggested.[35]

Third, we used methylprednisolone for 5 days only; recent studies suggested a beneficial effect when corticosteroid treatment was prolonged for more than 5 days in patients with community-acquired pneumonia.[14] Fourth, we did not set up rules

to reduce use or dosage of antibiotics according to clinical evolution and this might explain why we did not observe differences in the period of antibiotic treatment between the 2 groups.

Fifth, patient accrual was very slow, mainly due to the fact that nearly half (49%) of the patients with severe community-acquired pneumonia evaluated did not meet inclusion criteria. Sixth, the sample size calculation was based on a previous study performed in 15 hospitals[3] that used similar inclusion criteria as were used in the current trial. However, the treatment failure in the placebo group in this study (31%) was lower than in the control group in the earlier study. Given the observed treatment failure in our placebo group, the current study had less statistical power than predicted.

Another major limitation is the long duration of the study because the care of patients could have evolved during this time or many intervening diseases might have influenced the results. However, our protocol for managing patients with community-acquired pneumonia did not change during these years. We excluded patients with H1N1 influenza.

Time to the first antibiotic dosage was similar in both groups. In addition, we adjusted for the year of admission in the corresponding statistical models. Last, the small difference in the number of events (a difference of only 10 patients) indicates the need for study replication. A new trial is currently ongoing.[38]

Conclusions

Among patients with severe community-acquired pneumonia and high initial inflammatory response, the acute use of methylprednisolone compared with placebo decreased treatment failure. If replicated, these findings would support the use of corticosteroids as adjunctive treatment in this clinical population.

ARTICLE INFORMATION

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Author Contributions: Dr Torres had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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