Effects of systemic steroids in patients with severe community-acquired pneumonia

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ABSTRACT: The benefit of systemic steroids as adjunctive treatment in patients with severe community-acquired pneumonia (CAP) remains unclear. The present study aimed to evaluate the impact of corticosteroid treatment on mortality in patients with severe CAP.

A retrospective, observational study of a cohort of patients hospitalised with severe CAP, classes IV and V of the Prognostic Severity Index score, was carried out. Information on epidemiological, clinical and laboratory data, and 30-day mortality was collected from medical charts.

Of the 308 patients evaluated, 238 (77%) were treated with standard antimicrobial therapy and 70 (23%) received both antibiotics and systemic steroids. Clinical characteristics were similar between steroid and nonsteroid groups, except in the prevalence of male sex and the presence of chronic obstructive pulmonary disease. Systemic steroids were independently associated with a decreased mortality (odds ratio 0.287; 95% confidence interval 0.113–0.732), while severity of CAP (2.923; 1.262–6.770) was the only independent factor associated with increased mortality.

Mortality decreased in the patients with severe CAP who received simultaneous administration of systemic steroids along with antibiotic treatment.

Severity of community-acquired pneumonia remains the most important risk factor associated with increased mortality.

KEYWORDS: Community-acquired pneumonia, immune response, immunomodulation, mortality, systemic steroids

Community-acquired pneumonia (CAP) is a frequently occurring severe illness, the first infectious cause of death and the sixth cause of overall mortality in the developed world [1]. In Spain, the incidence of CAP in adults ranges 2–10 cases·1,000 habitants·yr^{-1}. This incidence increases to up 25–35 cases·1,000 habitants·yr^{-1} in people aged >70 yrs. At least 20% of patients with CAP will require hospitalisation and, of these, the mortality is ~10–25%, particularly in patients requiring intensive care unit (ICU) admission [2].

Despite more accurate aetiological diagnosis, effective antibiotic therapy and advances in supportive care, mortality rates of CAP remain similar to those reported >60 yrs ago [3] at the dawn of the antibiotic era. The study by AUSTRIAN and GOLD [4] showed that deaths occurring within the first 5 days of treatment were not due to failure to eradicate the microorganism; it suggested that they were due to an inappropriate response of the host.

Previous studies have shown increasing local and systemic inflammatory cytokine levels in patients with CAP [5–7] as a first step of the immune response to this infection. A fine balance between cytokine pro-inflammatory and anti-inflammatory activities has been shown to be critical in the host response. In this context, the modulation of the inflammatory response in severe CAP is an appealing concept and remains a matter of debate. Systemic steroids have an inhibitory effect on cytokine production, and have been proposed as a therapeutic option in pulmonary infection and severe sepsis, mainly in patients with adrenocortical insufficiency. However, information is lacking about the outcome of patients with severe CAP treated with both systemic steroids and antibiotics.

The aims of the present study were: 1) to determine predictive factors for mortality in the cohort of patients with severe CAP; and 2) to evaluate the impact on mortality of systemic steroid administration concomitant with antibiotic therapy at the time of CAP diagnosis.

MATERIALS AND METHODS
Study subjects
The study was performed at Hospital Mutua de Terrassa (Barcelona, Spain), an acute-care teaching institution with 25,000 admissions per year,

for a population of ~300,000 inhabitants. The current authors studied all adult patients with CAP who were admitted to hospital between October 1, 2001 and December 31, 2003.

CAP diagnosis was based on the presence of a new infiltrate on chest radiography in a patient with fever and/or leukocytosis when first seen in the Emergency Dept, or in the first 72 h of admission to hospital. The subset of patients selected were those with severe CAP, as defined by class IV and V of the prognostic severity index (PSI) reported by FINE et al. [8]. Patients were excluded if: 1) they had been hospitalised within the previous 14 days; 2) they were immunosuppressed (chronic use of systemic steroids (methylprednisone $\geqslant 24$ mg·day^{-1} or prednisone $\geqslant 30$ mg·day^{-1} $\geqslant 15$ days before the onset of pneumonia), nonsteroid immunosuppressive treatment or HIV); or 3) they had been given a diagnosis of tuberculosis, aspiration or obstructive pneumonia. The study was approved by the Ethical Committee of the current authors' institution.

Study design
The following variables were retrieved from the patients' medical charts: 1) demographic characteristics (age, sex and residence in a nursing home); 2) comorbidities; 3) clinical data on admission (body temperature, respiratory rate, cardiac frequency and arterial systolic and diastolic blood pressures); 4) laboratory and radiographical findings at admission; 5) PSI scores; 6) aetiology of pneumonia; 7) use of acute systemic corticosteroids; 8) ICU admission; 9) antimicrobial treatment; 10) days from diagnosis to death; and 11) early ($\leqslant 72$ h) and 30-day mortality. In chronic obstructive pulmonary disease (COPD) patients, spirometry results from the previous 3 yrs were recorded to evaluate severity of disease.

Methods
Comorbidity was measured using the Charlson Index [9]. This index was used to predict risk of death from comorbid disease. Presence of myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, COPD, autoimmune diseases, peptic ulcer, liver disease, diabetes mellitus, stroke, chronic renal failure, neoplasm, metastatic disease and HIV were included.

Neoplasm, liver disease and diabetes mellitus were specifically evaluated. COPD was defined by a previous clinical diagnosis of COPD, emphysema or chronic bronchitis, and forced spirometry showing forced expiratory volume in one second (FEV1) and FEV1/forced vital capacity <70% of their respective reference values. This could represent a possible confounding factor among patients treated with or without systemic steroids and was specifically included in the analysis.

Routine sampling to determine the aetiology of pneumonia included sputum, two sets of blood cultures, and urine for Streptococcus pneumoniae and Legionella pneumophila antigens. Detection of S. pneumoniae antigen in urine was performed by a rapid immunochromatographic assay (Now^{TM}; Binax, Portland, ME, USA). Detection of L. pneumophila serogroup I antigen in urine was performed by an immunoenzymatic commercial method (Legionella Urinary Antigen; Binax). Other additional diagnostic sampling techniques occasionally employed were pleural puncture, tracheobronchial aspirates and bronchoscopy with semiquantitative cultures of bronchoalveolar lavage.

Systemic steroid use was considered when dosages equivalent to methylprednisone $\geqslant 24$ mg·day^{-1} or prednisone $\geqslant 30$ mg·day^{-1} were given acutely at the time of diagnosis of CAP.

Analysis
Patients who were placed on systemic steroid therapy concomitant with the diagnosis of severe pneumonia were compared with those not receiving steroids at the time of diagnosis. A second analysis to determine factors related to mortality in the studied population was performed. In the descriptive analysis, percentages were used in categorical variables, mean$\pm$SD in continuous variables when normal distribution was assessed by the Kolmogorov–Smirnov test, and median (range) in the others. Univariate analysis was used to detect differences between groups and to identify potential risk factors for mortality. The Chi-squared or Fisher's exact test was used for categorical variables and an unpaired t-test or a nonparametric test (Mann–Whitney U-test) were used for continuous variables. Statistical significance was defined as p<0.05. Significant variables in the univariate analysis were further tested by means of logistic regression using the forward conditional method. Presence of COPD was included in the model despite its role as a confounding factor.

RESULTS
In total, 308 patients were hospitalised with severe CAP during the 26-month period of observation (210 in class IV, 98 in class V). Of these, 68.5% were male with a mean (range) age of 79.2 (25–100) yrs, and 237 (76.9%) were aged >70 yrs. Comorbidities were present in 275 (89.2%) patients, and the Charlson score was 2.49 (0–13). Of the patients, 49 (15.9%) had malignancy, 26 (8.4%) had liver disease and 61 (19.8%) were diabetic. There were 97 (31.5%) cases with the diagnosis of COPD who had a mean$\pm$SD FEV1 of 44.3$\pm$12.96%.

An aetiological diagnosis of CAP was made in 143 (46.4%) cases. S. pneumoniae was the most common offending microorganism (114 cases, 37%), followed by L. pneumophila (eight cases, 2.6%) and other microorganisms in the remaining 26 cases (8.4%).

In total, 18 (6%) patients died. Mortality was eight (3.8%) out of 210 and 10 (10.2%) out of 98 in class IV and V patients, respectively. Of the patients, 70 received systemic steroids while on antibiotic treatment (47 out of 210 class IV, 23 out of 98 class V). Patients received a median dose of methylprednisolone of 45.7 mg·day^{-1} or its equivalent, 11.4 (1–34) days from diagnosis. The indications for the administration of systemic steroid therapy are specified in table 1.

Age, comorbidity, concomitant illness, bacterial aetiology, hypotension and antimicrobial treatment of pneumonia were similar in both groups (table 2).

Male sex (p<0.001) and presence of COPD (p<0.001) were significant variables associated with the systemic steroid treatment group.

It is noteworthy that no differences in mean FEV1 values were found between COPD patients treated with or without corticosteroids. The most frequent reason for acute systemic steroid administration was bronchospasm. Mortality was similar in both groups.

TABLE 1 Indications for systemic steroid therapy

Indications	Subjects n
Broncospasm in chronic obstructive pulmonary disease patients	47
Broncospasm in patients without previous lung injury	14
Chronic asthma	2
Idiopathic pulmonary fibrosis	2
Unknown	5
Total	70

The characteristics of patients with severe CAP who died are shown in table 3. Only class V of PSI (p=0.007) was a significant risk factor associated with mortality in bivariate analysis (table 3). The current authors' logistic regression model (table 4) showed a protective role of steroid use (odds ratio (OR) 0.287; 95% confidence interval (CI) 0.113–0.732) and confirms severity of pneumonia (OR 2.923, 95% CI 1.262–6.770) as the only independent factor associated with increased mortality. Specifically, presence of COPD was not associated with a higher mortality rate. There was a trend of higher mortality in patients with the worst FEV1 values; however, differences were not significant.

Early mortality was observed in only two patients; neither had received steroids. Among the patients who died, mean time to death from pneumonia diagnosis was strikingly higher in patients treated with corticosteroids as compared with patients not treated with steroids (13.8 *versus* 7.1 days, p=0.005).

DISCUSSION

In the present study, treatment with systemic steroids reduced mortality in the cohort of patients with severe pneumonia. In fact, the present analysis suggests that patients with severe CAP receiving corticosteroid therapy and with equal Charlson score, ICU admission rates, monotherapy treatment, aetiology, PSI class and hypotension at admission do better than those not receiving steroid therapy.

The effects of steroids on the immune system are numerous, complex and not well understood [10]; consequently, it is very difficult to evaluate their effects on the immune response against infectious disease. Age, antimicrobial treatment,

TABLE 2 Characteristics of patients treated acutely with systemic steroids and antibiotics

	Acute systemic steroid administration		p-value
	No antibiotic treatment	Antibiotic treatment	
Subjects	238	70	
Age yrs	79.3±10.3	78.6±8.84	NS
Sex male	151 (63)	60 (85)	<0.001
Charlson index	2.32±1.7	2.5±1.6	NS
Comorbidities			
COPD	50 (21)	47 (67)	<0.001
Cancer	39 (16)	10 (14)	NS
Chronic liver disease	22 (9)	4(6)	NS
Diabetes mellitus	45 (19)	16(23)	NS
Mean of FEV1 in COPD patients	46.4±13.1	42.8±12.8	NS
ICU admission	9 (4)	2 (3)	NS
CAP treated with monotherapy	81 (34)	19 (27)	NS
CAP aetiology			NS
Streptococcus pneumoniae	88 (37)	26 (37)	
Legionella pneumophila	7 (3)	1 (1)	
Others	18 (8)	8 (11)	
Unknown	128 (53)	37 (53)	
Class V of PSI	74 (31)	23 (32)	NS
Hypotension	17 (7)	3 (4)	NS
Mortality	13 (5)	5 (7)	NS

Data are presented as n, mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; ICU: intensive care unit; CAP: community-acquired pneumonia; PSI: prognostic severity index; NS: nonsignificant.

TABLE 3	Epidemiological characteristics and mortality of patients with severe community-acquired pneumonia (CAP)		
	Mortality		**p-value**
	Yes	**No**	
Subjects	18	290	
Age yrs	79.9±8.5	79±9.9	NS
Sex male	13 (72)	198 (68)	NS
Charlson index	2.7±1.9	2.3±1.7	NS
Comorbidities			
COPD	5 (28)	92 (32)	NS
Cancer	3 (17)	46 (16)	NS
Chronic liver disease	3 (17)	23 (8)	NS
Diabetes mellitus	4 (22)	57 (20)	NS
Mean of FEV1 in COPD patients	37.7±10.2	44.6±13.0	NS
ICU admission	2 (11)	9 (3)	NS
CAP treated with monotherapy	7(39)	93 (32)	
CAP aetiology			NS
Streptococcus pneumoniae	6 (33)	108 (35)	
Legionella pneumophila	1 (6)	7 (3)	
Others	1 (0)	25 (9)	
Unknown	10 (55)	155 (53)	
Class V of PSI	10 (56)	87 (30)	0.007
Hypotension	1 (5)	19 (7)	NS
Systemic steroid treatment	5 (7)	65 (22)	NS

Data are presented as n, mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; ICU: intensive care unit; PSI: prognostic severity index; NS: nonsignificant.

TABLE 4	Risk factors for mortality in multivariate analysis
	OR (95% CI)
Systemic steroids	0.287 (0.113–0.732)
Severity of CAP	2.923 (1.262–6.770)
COPD	3.087 (0.906–7.031)

OR: odds ratio; CI: confidence interval; CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease.

steroid dose and its timing, comorbidity and aetiology of pneumonia are important variables to take into account when evaluating the impact of systemic steroids on outcome [11].

In the present cohort, all of these variables were equally represented among the groups. Only prevalence of COPD was significantly higher among patients on systemic steroids. Nevertheless, the mean value of FEV1 was similar between patients with and without steroid treatment. Data on COPD as a risk factor for increased mortality is conflicting [12–15]. It was included in the logistic regression model in order to determine whether COPD could be a confounding factor between mortality and steroid treatment. Even so COPD was not associated with mortality.

Recent studies have demonstrated the efficacy of systemic steroid treatment in patients with septic shock [16] or meningitis [17], but only a few dealing with severe CAP have been reported. Two studies suggest a beneficial effect of systemic steroids in severe CAP, but the characteristics of the population studied are quite different as compared with the present cohort. CONFALONIERI *et al.* [18] reported that a 7-day course of low-dose hydrocortisone infusion was associated with a significant reduction in duration of mechanical ventilation, length of hospital stay and hospital mortality in patients with CAP admitted to ICU. The inclusion of younger

(60.4 *versus* 77 yrs of age) patients and those with more severe disease (73.9 *versus* 4% requiring mechanical ventilation) differed markedly from the current cohort. In this setting, a recent report [19] on cortisol levels in patients with severe CAP admitted to the ICU showed that two-thirds had adrenal insufficiency. Clearly, the presence of underlying adrenal insufficiency could explain the favourable results obtained among some of the patients with severe pneumonia. Likewise, a second study by MONTÓN *et al.* [20] assessed the response of modulating therapy in mechanically ventilated patients only. The clinical characteristics of their patients were not reported but, again, severity of disease in these patients was significantly different as compared with the present cohort.

Glucocorticoids inhibit cytokines and other inflammatory molecules stimulated by bacterial infections that could be harmful to the host. However, the use of steroids also exerts a decisive influence in the immune function of macrophages and granulocytes, the main cell host defences against bacteria. It seems clear that precise knowledge of the subset of patients in whom steroids can improve the outcomes is yet to be defined. In this setting, information regarding the effect of corticosteroid use in patients who may have some kind of immunosuppression is lacking. Advances in the knowledge of cytokines release and kinetics, interferon-γ and granulocyte colony-stimulating factor, the most important cytokines in lung immune response [21–24], will permit a better understanding of the interaction between the endocrine and immune systems in respiratory infection and will make it possible to identify the subset of patients in whom steroid administration would be safe and effective.

The steroid dosage administered to the current patients was not focused on modulating sepsis [25, 26]. Currently, recommended steroid dosages used in sepsis are 50 mg·6 h^{-1} of hydrocortisone [16] (equivalence of one unit of hydrocortisone to five units of methylprednisolone [26]). By chance, the current patients received a median of 45.7 mg·24 h^{-1} of methylprednisolone, which is close to the recommended dose. Nevertheless, hydrocortisone has a more important mineral corticosteroid action. Another difference was the mean number of days on steroid treatment. The present patients were treated for a mean of 11.4 days, while 7 days was the standard duration of steroid treatment in sepsis [18]. This observation might be important because in the present study the patients treated with steroids died significantly later than patients without systemic steroid treatment (13.8 *versus* 7.1 days, p=0.005). Glucocorticoids exert a decisive influence in macrophage and granulocyte late function and, moreover, steroid

withdrawal may have a strong ''rebound'' effect in patients with severe infection [27]. The late mortality in steroid-treated patients suggests that the immune response to resolution of CAP and recovery of lung homeostasis could be seriously compromised by steroid administration at a late stage. A previous study suggests that the inflammatory response is attenuated in patients receiving long-term steroid treatment [28]. Consequently, in future studies to elucidate the role of glucocorticoids in severe CAP, it should be taken into account not only which subset of patients can potentially benefit from its administration, but also the optimal dose and duration of glucocorticoid treatment needed to achieve the proper balance between the beneficial and harmful effects of the inflammatory response.

An important limitation of the current study was that adrenocortical function was not studied in the group of patients treated acutely with systemic steroids. Another limitation was that administration of systemic steroids occurred at different times in the course of the disease. Timing of steroid administration might play a critical role because inflammatory response is a dynamic process and excessive modulation of any pathway could be the cause for an unwanted response. Ascertainment and selection bias, inherent to this design, were not thought to be a significant problem, due to the methodology used to identify patients and the fact that only a small amount of missing data was encountered.

Mortality was lower than expected as predicted by PSI [8]. Better standards of care, including systematic use of the therapeutic guidelines, could at least in partly explain these results. Exclusion of patients with aspiration pneumonia might also have contributed. As reported in a previous study [29], PSI should be considered a severity stratification index but not a good mortality predictor [8].

In conclusion, a better understanding of the interaction between systemic steroids and immune response is necessary before recommending their use in the treatment of severe community-acquired pneumonia. The current results are encouraging and suggest that the effects of systemic steroid administration as immunomodulating agents in an immunocompetent host with severe community-acquired pneumonia can decrease mortality. Further studies are needed to identify the subset of patients with severe pneumonia where systemic steroid administration can be beneficial and to detect the subset of patients in whom the use of steroids could be associated with poor outcomes.

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