Corticosteroid Therapy for Severe Community-Acquired Pneumonia: A Meta-Analysis

Ming Cheng MD, Zhi-yong Pan MD, Jiong Yang PhD, and Ya-dong Gao PhD

BACKGROUND: The debate about the efficacy of corticosteroids in the treatment of severe community-acquired pneumonia (CAP) is still a longstanding dilemma. We performed a meta-analysis including 4 randomized controlled trials (RCTs) to evaluate the effect of corticosteroids on the treatment of severe CAP in adults. METHODS: We performed a systematic review of published and unpublished clinical trials. Databases, including PubMed, Embase, CINAHL, and Cochrane (from their establishment to July 2013), were searched for relevant articles. Only RCTs of corticosteroids as adjunctive therapy in adult patients with severe CAP were selected. RESULTS: Four trials enrolling 264 patients with severe CAP were included. Use of corticosteroids significantly reduced hospital mortality compared with conventional therapy and placebo (Peto odds ratio = 0.39, 95% CI 0.17–0.90). The quality of the evidence underlying the pooled estimate of effect on hospital mortality was low, downgraded for inconsistency and imprecision. CONCLUSIONS: On the basis of the current limited evidence, we suggest that, although corticosteroid therapy may reduce mortality and improve the prognosis of adult patients with severe CAP, the results should be interpreted with caution due to the instability of pooled estimates. Reliable treatment recommendations will be raised only when large sufficiently powered multi-center RCTs are conducted. *Key words: severe cap; corticosteroids; mortality; meta-analysis.* [Respir Care 2014;59(4):557–563. © 2014 Daedalus Enterprises]

Introduction

Community-acquired pneumonia (CAP) is the most common infectious respiratory disease. In developed countries, it is the leading cause of death from infection and the sixth most prevalent cause of overall mortality, thus contributing to high economic and social costs.[1-3] Patients with severe CAP normally require mechanical ventilation (MV) and ICU admission. Despite remarkable advances in etiological investigation, antimicrobial therapy, and supportive measurements, the mortality of those patients still remains at ~50%.[4,5] Therefore, additional potential approaches are needed for better outcomes in severe CAP.

Recent studies found that the levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, IL-10, IL-1β, tumor necrosis factor alpha, and interferon gamma were significantly increased in patients with severe CAP and correlated with the severities and outcomes of CAP.[6-8] Appropriately producing cytokines in location play a role in inhibition and elimination of primary infection, but an excessive systemic and pulmonary inflammatory response in patients with severe CAP may contribute to injuries to the lung and other organs. This leads to sepsis, lung injury, and ARDS and is associated with poor prognosis and high mortality.[8-11] Therefore, downregulation of systemic inflammatory response may improve the clinical course of severe CAP.

Corticosteroids are known to be the most potent inflammatory inhibitors. They inhibit expression of pro-inflammatory cytokines and accelerate expression of anti-inflammatory cytokines.[12] The immunomodulating and anti-inflammatory pharmacodynamic profile is the physi-

Drs Cheng, Yang, and Gao are affiliated with the Department of Pneumology, and Dr Pang is affiliated with the Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan, People's Republic of China.

The authors have disclosed no conflicts of interest.

Correspondence: Ya-dong Gao, PhD, Department of Pneumology, Zhongnan Hospital of Wuhan University, Donghu Road 169, Wuhan 430071, People's Republic of China. E-mail: gaoyadong@hotmail.com.

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ologic rationale for their use in patients with severe infection. Furthermore, as the conception of critical illness-related corticosteroid insufficiency was put forward, steroid replacement therapy has been gradually accepted as a treatment for patients with critical illnesses.[13] By measuring random and cutoff levels of cortisol, Salluh et al[14] found that patients with severe CAP had a high prevalence of adrenocortical insufficiency. Another study reported that the baseline cortisol levels were positively correlated with disease severity scores, for example, APACHE II (Acute Physiology and Chronic Health Evaluation II); Sequential Organ Failure Assessment; and confusion, urea nitrogen, breathing frequency, blood pressure, ≥ 65 years of age (CURB-65). It has been suggested that baseline cortisol levels were better predictors of severity and outcome in patients with severe CAP than post-corticotropin cortisol levels or routinely measured laboratory parameters (C-reactive protein, leukocyte count, and D-dimer) and scores of severity.[15] Meduri et al[16] demonstrated in an in vitro study that methylprednisolone (MPDN) could decrease lung inflammatory response and lung bacterial burden. Nevertheless, the notion that corticosteroid treatment is beneficial to severe CAP has not currently reached a consensus. Three retrospective trials[17-19] and 2 randomized controlled trials (RCTs)[20,21] demonstrated no improved outcomes (clinical cures or survival) for patients receiving corticosteroids as adjunctive therapy. Moreover, the results of a systematic review[22] failed to confirm the effectiveness of corticosteroids in patients with severe CAP. In contrast, one meta-analysis[23] investigated the outcome of the administration of corticosteroids, especially prolonged therapy, and found that corticosteroid treatment was associated with reduced mortality in a subgroup of patients with severe CAP. Four RCTs[24-27] and one cohort study[28] concluded that corticosteroids combined with antibiotic therapy decreased mortality and improved outcomes of in-patients with severe CAP. Therefore, we conducted this meta-analysis to investigate the efficacy of corticosteroids in the management of severe CAP.

QUICK LOOK

Current knowledge

Community-acquired pneumonia (CAP) is the most common infectious respiratory disease. In developed countries, it is the leading cause of death from infection and the sixth most common cause of mortality. The role of corticosteroids in the treatment of CAP remains controversial.

What this paper contributes to our knowledge

Corticosteroid therapy appears to reduce mortality and to improve the prognosis of adults with CAP. The instability of pooled estimates suggests that treatment recommendations should await sufficiently powered multicenter randomized controlled trials.

Methods

The study was performed at Zhongnan Hospital of Wuhan University, Wuhan, People's Republic of China.

Search Strategy

A literature search was performed independently by 2 investigators to identify RCTs from the following databases: PubMed, Embase, CINAHL, and Cochrane (from their inception to July 2013). The key words used were "severe CAP," "corticosteroids," "steroids," "methylprednisolone," and "hydrocortisone." We also reviewed the bibliographies and reference lists through a manual search of citations from retrieved articles to identify other potentially eligible studies.

Selection Criteria

For this meta-analysis, studies meeting the following criteria were included: (1) only studies designed as RCTs, (2) adult patients with severe CAP as participants, (3) intervention with corticosteroids used as adjunctive therapy for patients with severe CAP, (4) control intervention with placebo (normal saline solution or drugs with a physical appearance similar to corticosteroids), and (5) hospital mortality as the primary outcome. We excluded studies based on the following criteria: (1) studies enrolling pediatric patients or nosocomial pneumonia patients, (2) studies having only abstracts without full text, and (3) studies lacking adequate original data.

Quality Assessment

Two investigators assessed the eligibility and quality of selected studies blinded to each other and resolved any disagreement by consensus. We chose the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria to assess the quality of each randomized clinical trial. Following the GRADE recommendation, the classification of evidence quality consisted of high, moderate, low, and very low. The quality of RCTs was considered high, but it may be downgraded by the following factors: methods of randomization, allocation concealment, blinding, whether the analysis respected the intention-to-treat principle, and whether trials avoided the risk associated with stopping for perceived benefit.

Data Extraction

Data extraction was performed independently by 2 investigators from each study, and relevant information consisted of the following: first author, year of publication, study design, number of patients, participant demographics, diagnostic criteria of severe CAP, corticosteroid treatment (drug, dose, and duration), and outcome variables. We contacted authors through e-mail to obtain key study details when needed. Any disagreements were resolved by iteration and consensus.

Quantitative Data Synthesis

Hospital mortality or, when that information was unavailable, mortality at the longest follow-up time was chosen as the primary end point. Secondary outcomes were length of hospital stay, length of ICU stay, duration of MV, days off MV, and adverse effects. Those outcomes were analyzed on an intention-to-treat basis. We pooled study results of the common odds ratio (OR) and risk differences with a 95% CI using a Peto model.[29] Heterogeneity among studies was evaluated by Cochran's Q test and I^2 statistics. If significant heterogeneity was shown ($P < .1$, $I^2 > 50\%$), a random-effects model was selected; otherwise a fixed-effects model was used. Based on a Cochrane recommendation, heterogeneity was classified as low ($\leq 25\%$), moderate (25–50%), and high ($> 50\%$). We calculated the presence of publication bias using funnel plots.[30] Statistical analysis was performed using the Review Manager 5.0 software (Cochrane Collaboration).

Results

Trial Flow

The literature search yielded 6,172 citations initially. We excluded 6,158 citations because they were duplications, the studies were not RCTs, or they were not related to CAP. After reviewing 14 full-text citations, 4 observational studies[17-19,31] and one commentary[32] were excluded. Thus, 9 RCTs about corticosteroid therapy for CAP met our inclusion criteria (Fig.1). We excluded 3 trials because they investigated patients with mild-to-severe CAP without classification.[33-35] Another trial[27] was excluded because it evaluated patients with a wide spectrum of severity (from classes I to V) but did not present mortality data in a subgroup of patients with severe CAP. At last, we decided to exclude the study by Marik et al[20] from the analysis because its design was different from the other studies in that a single dose of corticosteroids prior to antibiotic therapy was used.

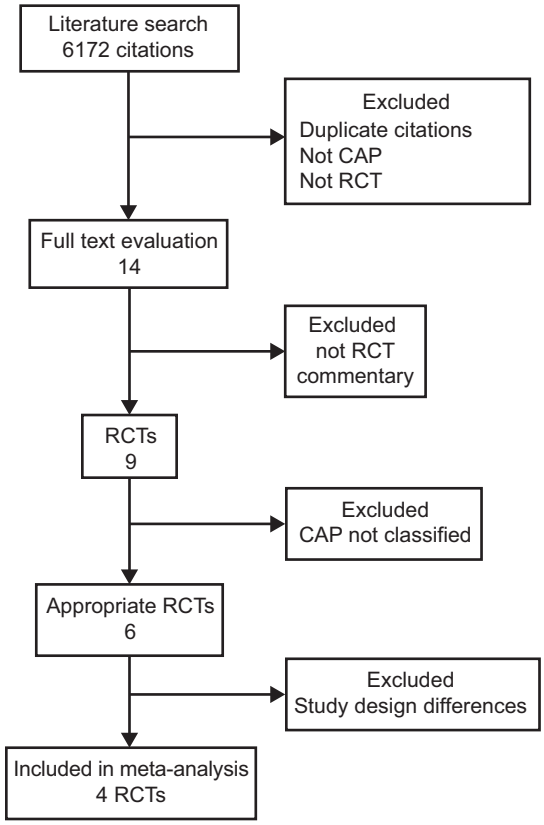

Fig. 1. Inclusion criteria flow chart. CAP = community-acquired pneumonia; RCT = randomized controlled trial.

Study Characteristics

Table 1 presents the main characteristics of 4 trials included in this review. In total, there were 134 individuals in the intervention group and 130 individuals in the control group. Among these trials, one study[25] enrolled patients with mild-to-severe CAP, but it separately conducted a subanalysis of clinical outcomes of severe pneumonia, as defined by a CURB-65 score of ≥ 3 or a Pneumonia Severity Index score of ≥ 4. Corticosteroids used in these trials included hydrocortisone, prednisolone, and MPDN. The duration of corticosteroid therapy ranged from 7 to 9 d (in 3 studies, 7 d; in one study, 9 d).

Quantitative Data Synthesis

We summarized the pooled results of the 4 trials (Fig. 2). There was moderate heterogeneity among study results ($P = .14$, $I^2 = 46\%$). Mortality of patients treated with corticosteroids was significantly lower than that of patients with placebo (Peto OR = 0.39, 95% CI 0.17–0.90). Table 2 shows secondary outcomes. These data suggest that therapy with corticosteroids may improve the prognosis of adult patients with severe CAP.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Reference and Authors	Study Design	Patients (*n*; Intervention/ Control)	Mean Age (y)	Severe Criterion	Corticosteroids Used	Placebo
Confalonieri et al[24]	DB, RCT, MC	23/23	64	1993 ATS	Hydrocortisone, 240 mg/d, 7 d	Sterile normal saline
Fernandez-Serrano et al[21]	DB, RCT, SC	23/22	63	Unclear	MPDN, 620 mg, 9 d	Drugs with similar physical appearance to corticosteroids
Sabry and Omar[26]	DB, RCT, MC	40/40	62	1998 ATS	Hydrocortisone, 300 mg/d, 7 d	Normal saline solution
Snijders et al[25]	DB, RCT, SC	48/45	63	CURB-65 (score > 2)	Prednisolone, 40 mg/d, 7d	Unclear

DB = double-blind
RCT = randomized controlled trial
MC = multi-center
MPDN = methylprednisolone
SC = single center
ATS = American Thoracic Society
CURB-65 = confusion, urea nitrogen, breathing frequency, blood pressure, ≥ 65 years of age

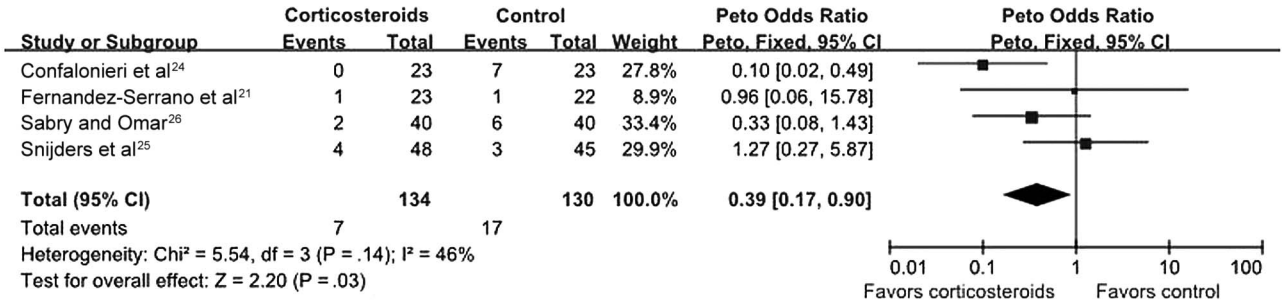

Fig. 2. Correlation between mortality and corticosteroid treatment. df = degrees of freedom.

Table 2. Effects of Corticosteroids vs Placebo on Different End Points of Severe CAP Studies

Reference and Authors	Length of ICU Stay (d)	Length of Hospital Stay (d)	Duration of MV (d)	Days off MV	Adverse Effects
Confalonieri et al[24]	10 (4–33)* vs 18 (3–45)*, *P* = .01	13 (10–53)* vs 21 (3–72)*, *P* = .03	4 (1–27)* vs 10 (2–44)*, *P* = .007		*n* of patients with polyneuropathy of critical illness: 0 vs 3/23 (*P* = .2) *n* of patients with gastrointestinal bleeding: 1/23 vs 1/23 (*P* = 1.0)
Fernandez-Serrano et al[21]	6.5 (5.5–9)* vs 10.5 (6.25–24.5)*	10 (9–13)* vs 11.5 (9–14)*	3 vs 13 (7–26)*		Not reported
Sabry and Omar[26]				3.4 (0.58)† vs 1.2 (0.42)†, *P* = .01	Ratio of patients with upper gastrointestinal bleeding: 5% vs 5%; patients with delayed septic shock: 5% vs 35%
Snijders et al[25]		19.4 (20.2)† vs 20.4 (22.7)†, *P* = .87			Not reported

* Data are reported as median (range).
† Data are reported as mean (SD).
CAP = community-acquired pneumonia
MV = mechanical ventilation

Table 3. Risk of Bias Summary of Included Studies

Reference and Authors	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Confalonieri et al[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Fernandez-Serrano et al[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sabry and Omar[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Snijders et al[25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Sensitivity Analysis and Publication Bias

A sensitivity analysis was carried out by the sequential dropping of each study. Significant differences were observed for 2 studies, resulting in no significant mortality reduction. Although the study by Confalonieri et al[24] had a heavy weight of 27.8%, when excluded from the data, the pooled result showed no effect of corticosteroids in patients with severe CAP (Peto OR = 0.66, 95% CI 0.25–1.77), and heterogeneity was considerably reduced ($I^2 = 0\%$). Similarly, when the study by Sabry and Omar[26] was dropped, the results also changed significantly, with common Peto ORs of 0.42 (95% CI 0.15–1.18; weight = 33.4%).

Publication bias was not assessed because of the limited number (< 10) of studies included in this analysis.

Discussion

This is the first meta-analysis of RCTs to evaluate the outcome of corticosteroids as adjunctive therapy in adult patients with severe CAP. Unlike the systematic review by Salluh et al,[22] all eligible trials we included were double-blinded RCTs with high quality. Table 3 shows the risk of bias varying across trials. Double-blinded RCTs were assigned to a low risk of bias. Our analysis suggests that corticosteroids may reduce overall mortality and improve the outcomes of patients with severe CAP. Recently, Nie et al[23] performed a meta-analysis of RCTs to assess the benefits and risks of corticosteroids in the treatment of CAP in adults. They showed that a benefit was not found for corticosteroid treatment of patients with CAP, but analyses restricted to severe CAP patients or prolonged corticosteroid treatment showed a survival benefit. A retrospective cohort study conducted by Garcia-Vidal et al[28] pointed out that mortality decreased in the patients with severe CAP who received steroids along with antibiotic treatment. Mikami et al[27] demonstrated that a short course of low-dose corticosteroids administered to patients with moderate-to-severe CAP promoted the resolution of clinical symptoms and reduced the duration of intravenous antibiotic therapy. In a retrospective study about the efficacy of MPDN therapy in patients with severe pneumonia, Kiyokawa and Kawai[31] suggested that the administration of steroids in the early stage after the onset of pneumonia could increase the average cure rate.

However, the findings of the present study must be viewed in the context of potential limitations. First, the sensitivity analysis revealed the instability of pooled estimates due to the limited number of studies included, which reflected substantial heterogeneity among those studies. In this study, the instability was associated with differences in corticosteroid administration, antibiotic therapy, characteristics of population, definition of severe CAP, and study design. Two trials[24,26] used hydrocortisone, and the other two used prednisolone[25] and MPDN.[21] All studies used long-course treatment, 7 d in 3 trials[24-26] and 9 d in one trial.[21] In addition, the choice and dose of antibiotics may influence results. Only one study overcame this problem by administering the same antibiotics (ceftriaxone plus levofloxacin).[21] Second, this study lacked the power to test publication bias because of the limited number (< 10) of trials included. In the study by Confalonieri et al,[24] 7 patients died in the control group, but none died in the intervention group, which may generate high publication bias. Importantly, the small sample size, a common problem in 4 studies, may have biased their results. Moreover, this meta-analysis lacked pooled effect to detect potentially significant harmful effects because of a relatively small number of included trials. Only 2 trials reported adverse effects, including gastrointestinal bleeding, polyneuropathy of critical illness, and delayed septic shock.[24,26] Snijders et al[25] did not report adverse effects in patients with a CURB-65 score of > 2. Finally, various types, dosages, and durations of corticosteroids were used in the 4 trials. In addition, the diagnosis criteria of severe pneumonia were not exactly the same in these trials. So far, there are only a few reports regarding steroid dosage and duration in pneumonia patients. Nie et al[23] found that prolonged corticosteroid treatment for severe CAP provided a survival benefit. Mikami et al[27] reported that administration of short-course and low-dose corticosteroids promoted improvement in major symptoms and shortened the duration of antibiotic treatment. Kiyokawa and Kawai[31] found that the total dose of steroids given within 7 d was lower in cured cases (774 $\pm$ 749 mg) than in non-cured cases (1,190 $\pm$ 768 mg) ($P < .05$). This indicated that there was

an association between corticosteroid dose and severity of pneumonia. Given the critical flaws outlined above, the benefit of corticosteroid treatment in adult patients with severe CAP should be viewed with caution. Therefore, large-scale and well-designed RCTs are urgently needed. In future studies, the drug used, duration of therapy, dose of corticosteroids, and adverse effects also should be given more attention.

Conclusion

On the basis of the current limited evidence, we suggest that, although corticosteroid therapy may reduce mortality and improve the prognosis of adult patients with severe CAP, the results should be interpreted with caution due to the instability of pooled estimates. Reliable treatment recommendations will be raised only when large sufficiently powered multi-center RCTs are conducted.

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