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Corticosteroid therapy for severe community-acquired pneumonia: A meta-analysis

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Abstract

Background The debate about the efficacy of corticosteroids in the treatment of severe community-acquired pneumonia (CAP) is still a long-standing dilemma. We did a meta-analysis including four randomized controlled trials (RCTs) to evaluate the effect of corticosteroids on the treatment of severe CAP of adults.

Methods We performed a systematic review of published and unpublished clinical trails. Databases including PubMed, CENTRAI, CINAHL and Cochrane (from their establishment to July 2013) were searched for relevant literatures. Only RCTs of corticosteroids as adjunctive therapy in adult patients with severe CAP were selected.

Results Four trails enrolling 264 severe CAP patients were included. Use of corticosteroids significantly reduced hospital mortality compared with conventional therapy and placebo (Peto OR=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 Based on 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 multicenter RCTs are conducted.

Key words: severe CAP; corticosteroids; mortality; meta-analysis

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1 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, which contributes to high economical and social costs[1-3]. Patients with severe CAP normally require mechanical ventilation (MV) and intensive care unit (ICU) admission. Despite remarkable advances in etiological investigation, antimicrobial therapy and supportive measurements, the mortality of those patients still stays at about 50%[4, 5]. Therefore, additional potential approaches should be searched for better outcomes of severe CAP.

Recent studies found that the levels of proinflammatory cytokines such as interleukin (IL)-6, IL-8, IL-10, IL-1β, tumor necrosis factor (TNF)-α and interferon (INF)-γ were significantly increased in severe CAP, and correlated with the severities and outcomes of CAP[6-8]. Appropriate produced cytokines in location play a role in inhibition and elimination of primary infection, but an excessive systemic and pulmonary inflammatory response in severe CAP may contribute to lung and other organs injury. This leads to sepsis, lung injury and acute respiratory distress syndrome (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 physiological rationale for their use in severe infections. Furthermore, as the conception of critical illness-related corticosteroid insufficiency (CIRCI) proposed, steroids replacement therapy has been gradually accepted in critical illness[13]. Salluh *et al.* found that patients with severe CAP had the high prevalence of adrenocortical insufficiency by measuring random and cutoff levels

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cortisol respectively[14]. Another study reported that the baseline cortisol levels were positive correlated with disease severity scores, e g, acute physiology and chronic health evaluation II (APACHE II), acute physiology and chronic health evaluation (SOFA), and confusion, urea nitrogen, respiratory rate, BP, age > 65 years (CURB-65). It is suggested that baseline cortisol levels were better predictors of severity and outcome in severe CAP than postcorticotropin cortisol or routinely measured laboratory parameters (C-reactive protein, leukocyte count, and d-dimer) and scores of severity[15]. Meduri M *et al.* demonstrated in an *in vitro* study that methylprednisolone (MPDN) could decrease lung inflammatory response and lung bacterial burden[16]. Nevertheless, it has not currently reached a consensus that corticosteroid treatment is beneficial to severe CAP. Three retrospective trails[17-19] and two RCTs[20, 21] demonstrated no improved outcomes (clinical cures or survival) in patients receiving corticosteroids as adjunctive therapy. Moreover, results of a systematic review[22] failed to confirm the effectiveness of corticosteroids in severe CAP. In contrast, one meta-analysis investigated the outcome of the administration of corticosteroids, especially prolonged therapy, and found that corticosteroid treatment was associated with reduced mortality in subgroup of severe CAP[23]. Four RCTs[24-27] and a cohort study[28] concluded that corticosteroids combined with antibiotic therapy decreased mortality and improved outcomes of inpatients of severe CAP. Therefore, we conducted this meta-analysis to investigate the efficacy of corticosteroids in the management of severe community-acquired pneumonia.

2 Materials and Methods

2.1 Search strategy

A literature search was performed by two investigators independently to identify randomized controlled trails from following databases: PubMed, CENTRAI, 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

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citations from retrieved articles to identify other potentially eligible studies.

2.2 Selection criteria

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

2.3 Quality assessment

Two investigators assessed the eligibility and quality of selected studies blinded to each other and resolved any disagreement by consensus. We chose Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria to assess the quality of each randomized clinical trails. Following GRADE recommendation, the classification of evidence quality was high, moderate, low and very low. Quality of RCTs was considered high, but it may be downgraded by 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.

2.4 Data extraction

Data extraction was performed independently by two investigators from each study, and relevant information contained: first author, year of publication, study design, number of patients, participant demographics, diagnostic criteria of severe CAP, corticosteroids 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.

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2.5 Quantitative data synthesis

Hospital mortality, or when unavailable, mortality at the longest follow-up time was chosen as primary endpoint. Secondary outcomes were length of hospital stay, length of ICU stay, duration of MV, days off MV and adverse effects. These outcomes were analyzed on an 'intention-to-treat (ITT)' basis. We pooled study results of the common odds ratio (OR) and risk differences with a 95% confidence interval (CI) using a Peto model[29]. Heterogeneity among studies was evaluated by Cochran Q test and I^2 statistics. If significant heterogeneity was shown ($P<0.1$ or I^2 >50%), a random-effects model was selected, otherwise a fixed-effects model was used. Based on Cochrane recommendation, heterogeneity was classified as low (<=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).

3 Results

3.1 Trial flow

The initial literature search yielded 6172 citations. We excluded 6158 citations due to duplication, not RCTs and no related to CAP. After reviewing 14 full-text citations, four observational studies[17-19, 31] and a 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 from mild to severe CAP without classification[33-35]. Another trial was excluded since it evaluated patients with a wide spectrum of severity (from classes I to V) but did not present mortality data in subgroup of severe CAP[27]. At last, we decided to exclude Marik's study from the analysis because its design was different form the others', using a single dose of corticosteroids prior to antibiotic therapy[20].

Figure 1 Flow diagram.

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3.2 Study characteristics

Table 1 presents the main characteristics of four 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 enrolled mild to severe CAP patients, but it separately conducted a subanalysis of clinical outcome of severe pneumonia as defined by CURB-65 score of 3 or more or PSI score of 4 or more[25]. Corticosteroids used in these trials included hydrocortisone, prednisolone, and methy-prednisolone (MPDN). The duration of corticosteroids therapy ranged from 7 to 9 days (three studies=7 days, and one study=9 days).

3.3 Quantitative data synthesis

We summarized the pooled results of the 4 trials (Fig. 2). There was moderate heterogeneity among study results (P=0.14, I^2 = 46%). Mortality for patients treated with corticosteroids was significantly lower than that in patients with placebo (Peto OR, 0.39; 95% CI, 0.17-0.90). Table 2 shows secondary outcomes. These data suggest that corticosteroids may improve the prognosis of adult patients with severe CAP.

Figure 2. The correlation between mortality and the treatment with corticosteroids**.**

3.4 Sensitivity analysis and publication bias

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

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

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4 Discussion

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

However, the findings of the present study must be viewed in the context of potential limitations. First, the sensitivity analysis revealed instability of pooled estimates due to the limited number of studies included, which reflected substantial heterogeneity among these studies. Not surprisingly, it was associated with the differences in corticosteroids administration, antibiotic therapy, characteristics of populations, definition of severe CAP and study design. Two trails[24, 26] used hydrocortisone, and the other two used prednisolone[25] and MPDN[21] respectively. All studies used long-course treatment, 7 days in three trials[24-26] and 9 days in one[21]. In addition, the choice and dose of antibiotics may influence results. Only one study

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overcame this problem by giving the same antibiotics (ceftriaxone plus levofloxacin)[21].Second, this meta-analysis lacked power to test publication bias since limited number (<10) of included trials. In the study by Confalonieri *et al.*, 7 patients died in the control group but 0 in the intervention group that may generate high publication bias[24]. 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, delayed septic shock[24, 26]. Snijders *et al.* did not report adverse effects in patients with CURB-65 score > 2[25]. Finally, various type, dosage and duration of corticosteroids were used in the 4 trials. In addition, the diagnosis criteria of severe pneumonia were not exactly same in these trials. So far, there are only a few reports regarding steroid dosage and duration to pneumonia patients. Wei *et al.* indicated that prolonged corticosteroids treatment showed a survival benefit in severe CAP[23]. Mikami *et al.* reported that administration of short-course and low-dose corticosteroids promoted improvement in major symptoms and shortened the duration of antibiotic treatment[27]. Kiyokawa *et al.* found that the total dose of steroids given within 7 days was less in cured cases (774 ± 749 mg) than in non-cured cases (1,190 ± 768 mg) ($P<0.05$)[31]. This indicated that there was an association between corticosteroid dose and severity of pneumonia. Given the critical flaws outlined above, the benefit of corticosteroids treatment in adult patients with severe CAP should be viewed with caution. Therefore, large-scale and well-designed RCTs are urgently needed. In the future studies, the drug, duration, dose of corticosteroids and adverse effects also should be given more attention.

5. Conclusion

Based on 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

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estimates. Reliable treatment recommendations will be raised only when large sufficiently powered multicenter RCTs are conducted.

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Reference (auther/year)	Study Desgin	No.Patients (Intervention/control)	Mean Age(y)	Severe criterion	Corticosteroids Used	Placebo
Confalonieri[24] /2005	DB RCT MC	23/23	64	1993 ATS	Hydrocortisone, 240mg/d,7d	Sterile normal saline
Fernandez-Serrano[21] /2011	DB RCT SC	23/22	63	Unclear	Methyl-prednisone 620mg,9d	Drugs with similar physical appearance to corticosteroids
Sabry[26] /2011	DB RCT MC	40/40	62	1998 ATS	Hydrocortisone, 300mg/d,7d	Normal saline solution
Snijlers[25] /2010	DB RCT SC	48/45	63	CURB-65 (score>2)	Prednisolone, 40mg/d,7d	Unclear

Table 1. Characteristics of the studies included in the meta-analysis

DB: double-blind; RCT: randomized controlled trial; MC: multicenter; SC: single center; ATS: American Thoracic Society; CURB: severity index for community-acquired pneumonia evaluating Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older

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Reference	Length of ICU stay (days)	Length of hospital stay (days)	Duration of MV (days)	Days off mechanical ventilation	Adevrse effects
Confalonieri[24] /2005	10(4-33)* versus 18(3-45)* p=0.01	13(10-53)* versus 21(3-72)* p=0.03	4(1-27)* versus 10(2-44)* P=0.007		Number of patients with polyneuropathy of critical illness: 0 versus 3/23 (P =0.2) Number of patients with a gastrointestinal bleed: 1/23 versus 1/23 (P = 1.0)
Fernandez-Serrano[21] /2011	6.5(5.5-9)* versus 10.5(6.25-24.5)*	10(9-13)* versus 11.5(9-14)*	3 versus 13(7-26)*		Not reported
Sabry[26] /2011				3.4(0.58)$ versus 1.2(0.42)$ p=0.01	Raito of patients with upper gastrointestinal bleeding : 5% versus 5%; Patients with delayed septic shock:5% versus 35%
Snijlers[25] /2010		19.4(20.2)$ versus 20..4(22.7)$ p=0.87			Not reported

Table 2 Effects of corticosteroids versus placebo on different endpoints of severe community-acquired pneumonia studies

$ data are reported as mean(SD) , * data are reported as median (range)

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Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Confalonieri[24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Fernandez-Serrano[21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sabry[26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
Snijlers[25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 3 Risk of bias summary of included studies.

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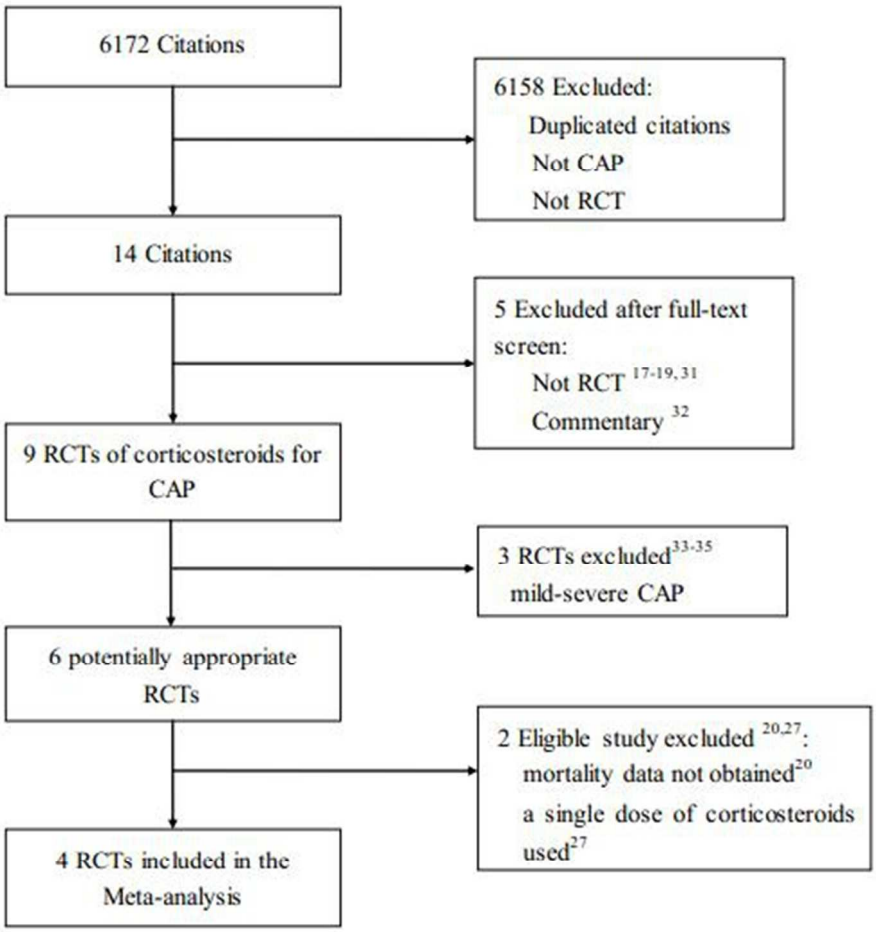

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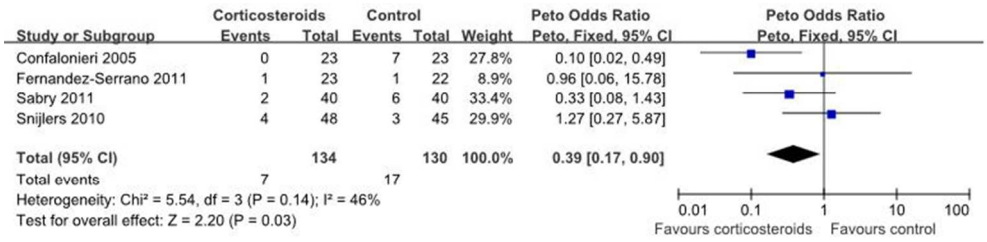

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