CHEST

Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia

A Systematic Review and Meta-Analysis

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BACKGROUND: Corticosteroids are an option in the treatment of community-acquired pneumonia (CAP). However, the benefits and adverse effects of corticosteroids, especially in severe CAP, have not been well assessed.

METHODS: PubMed, Embase, and Cochrane library databases from inception to May 2015 were searched. Randomized controlled trials (RCTs) and cohort studies that evaluated use of corticosteroids in adult patients with CAP were included. The quality of outcomes was evaluated using Grading of Recommendations Assessment, Development and Evaluation methodology. The Mantel-Haenszel method with random-effects modeling was used to calculate pooled relative risks (RRs) and 95% CIs.

RESULTS: Nine eligible RCTs (1,667 patients) and six cohort studies (4,095 patients) were identified. The mean corticosteroid dose and treatment duration were 30 mg/day methylprednisolone for 7 days. Corticosteroids did not have a statistically significant effect on mortality (RR, 0.72; 95% CI, 0.43-1.21; evidence rank, low) in patients with CAP and patients with severe CAP (RCTs: RR, 0.72; 95% CI, 0.43-1.21; evidence rank, low; cohort studies: RR, 1.00; 95% CI, 0.86-1.17). Corticosteroids treatment was associated with a decreased risk of ARDS (RR, 0.21; 95% CI, 0.08-0.59) and may reduce lengths of hospital and ICU stay, duration of IV antibiotic treatment, and time to clinical stability. Corticosteroids were not associated with increased rates of adverse events.

CONCLUSIONS: Short-term treatment with corticosteroids is safe and may reduce the risk of ARDS, shortening the length of the disease in patients with CAP.

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KEY WORDS: C-reactive protein; community-acquired pneumonia; critical care

ABBREVIATIONS: CAP = community-acquired pneumonia; GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trials; RR = relative risk

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Community-acquired pneumonia (CAP) is a common and serious infectious disease and one of the leading causes of death in low-income countries.[1] Despite advances in antibiotic treatment, mortality rates in patients with CAP remain high, up to 40% in patients with severe CAP.[2]

Corticosteroids are anti-inflammatory agents frequently used to treat CAP in clinical practice.[3] Corticosteroids inhibit the expression and action of many cytokines involved in the inflammatory response associated with pneumonia. In multicenter randomized clinical trials, corticosteroids were found to reduce treatment failure rate,[4] shorten time to clinical stability,[5] and reduce the length of hospital stay.[6] Additionally, a meta-analysis[7] found that treatment with corticosteroids was associated with improved mortality rates in patients with severe CAP. However, a large observational study,[3] involving 6,925 patients, found that corticosteroids had a possible survival advantage in patients with septic shock, complicating CAP, but not in patients with severe CAP without shock. Thus, findings showing that corticosteroids reduce mortality may be due to the overinclusion of patients with septic shock or with other conditions known to benefit from corticosteroid treatment, including COPD and asthma.

This systematic review and meta-analysis, including data from the latest published randomized controlled trials (RCTs) and cohort studies, was performed to evaluate the effect of corticosteroid therapy on important outcomes in patients with CAP. It was of particular interest to determine whether corticosteroids enhanced survival outcomes in patients with severe CAP.

Methods

This systematic review and meta-analysis was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[8] The methodology was based on recommendations from the Cochrane Collaboration; the results were evaluated according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines.[9]

Literature Search and Study Selection

The PubMed, Cochrane, and Embase databases were searched for data from May 1950 to May 2015 to identify all trials assessing corticosteroid therapy for patients with CAP (see details of the search strategy in e-Appendix 1).

Studies were included if they were RCTs assessing corticosteroid treatment in adult patients with CAP, compared with placebo or no agent, and had mortality rate, either in-hospital or 28-day mortality. Observational studies were included to confirm the results of RCTs. Studies published in abstract form were included in the sensitivity analyses.

Data Extraction

Using preprepared extraction forms, two researchers independently recorded the characteristics of the trials, interventions, and outcomes. The predefined primary outcome was mortality. Secondary outcomes were adverse events (hyperglycemia, superinfection, GI bleeding, empyema, and ARDS) and efficacy outcomes (length of hospital stay, length of ICU stay, duration of IV antibiotic treatment, time to clinical stability, and readmission to hospital).

Risk of Bias Assessment

As recommended by the Cochrane Collaboration,[10] domains of bias of the studies included for efficacy results were reviewed, including random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other biases. Other biases included the balance among patients with shock, asthma, COPD, and severe CAP; whether the trial was terminated early; and sponsor bias. Domains of bias of the studies included for adverse events were also reviewed.[11] The studies that fulfilled more than six, four to six, and fewer than items were defined as being of high, fair, and poor quality, respectively.

The quality of evidence for mortality and adverse events was evaluated according to GRADE methodology. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were evaluated and classified as very low, low, moderate, or high.[9]

Statistical Analysis

Mantel-Haenszel random-effects meta-analyses were performed for the RCTs and observational studies. All statistical analysis was performed using Review Manager (RevMan), version 5.3 (Cochrane Collaboration); STATA 12.0 (Stata Corp); and trial sequential analysis program, version 0.9 beta (www.ctu.dk/tsa).[12]

Predefined subgroup analyses were performed according to the severity of CAP, inflammatory response, use of a loading dose, effective pharmacological effect reached, type of mortality, duration of corticosteroid treatment, cumulative dose of corticosteroids, and effects model. The stability of the results was confirmed by sensitivity and trial sequence analyses (see e-Appendix 2).

Results

Characteristics of Studies

The initial search yielded 336 citations; nine RCTs[4-6,13-18] that randomized 1,667 patients and six cohort studies[3,19-23] involving 4,095 patients were included in the meta-analysis (e-Figure 1). No study in abstract form was found.

The characteristics of the RCTs are listed in Table 1, and their efficacy outcomes are shown in Table 2. Four studies involved patients with severe CAP, with a

TABLE 1] Characteristics of Included RCTs

Study	Design, Country	No. of Patients (Corticosteroids/ Control)	Patient Selection	Corticosteroids	Dose	Period, d	Cumulative Dose (as Equivalent Dose of Methylprednisolone), mg	CRP Level (Corticosteroids/ Control), mg/L	Severity of Illness (Corticosteroids/ Control)
Torres et al, 2015[4]	Three centers, RCT, Spain	120 (61/59)	Severe CAP with a high inflammatory response	Methylprednisolone	IV bolus, 0.5 mg/kg/ 12 h	5	425 (set as 85 kg)	273 (202-292)/244 (172-289)	PSI VI-V (% of total) (70/79)
Blum et al, 2015[5]	Seven centers, RCT, Switzerland	785 (392/39)	Mild, moderate, and severe CAP	Prednisone	Oral, 50 mg/d	7	280	159 (80-245)/ 164 (79-250)	PSI VI-V (% of total) (52/47)
Nafae et al, 2013[13]	Single center, RCT, Egypt	80 (60/20)	Mild, moderate, and severe CAP	Hydrocortisone	IV loading bolus dose, 200 mg, then infusion, 240 mg/ d (10 mg/h)	7	376	91 ± 40/95 ± 46 mg/dL	NA
Meijvis et al, 2011[6]	Two centers, RCT, Netherlands	304 (151/153)	Mild to severe CAP	Dexamethasone	IV bolus, 5 mg/d	4	107	225 ± 144/ 210 ± 137	PSI VI-V (% of total) (53/42)
Fernández-Serrano et al, 2011[14]	Single center, RCT, Spain	56 (28/28)	Severe CAP	Methylprednisolone	IV loading bolus dose, 200 mg, then IV dose, 20 mg/6 h, 20 mg/12 h, and 20 mg/ day for 3 days, respectively	9	620	NA	SAPS 8 (5-12)/7 (6-12)
Snijders et al, 2010[15]	Single center, RCT, Netherlands	213 (104/109)	Mild to severe CAP	Prednisolone	40 mg/d	7	224	259 ± 154/ 215 ± 144	PSI VI-V (% of total) (46/41)
Mikami et al, 2007[16]	Single center, RCT, Japan	31 (15/16)	Mild to severe CAP	Prednisolone	40 mg/d	3	96	20 ± 9/19 ± 7 mg/dL	PSI VI-V (% of total) (60/50)

(Continued)

TABLE 1] (Continued)

Study	Design, Country	No. of Patients (Corticosteroids/ Control)	Patient Selection	Corticosteroids	Dose	Period, d	Cumulative Dose (as Equivalent Dose of Methylprednisolone), mg	CRP Level (Corticosteroids/ Control), mg/L	Severity of Illness (Corticosteroids/ Control)
Confalonieri, 2005[17]	Six centers, RCT, Italy	48 (24/24)	Severe CAP	Hydrocortisone	IV loading bolus, 200 mg, then IV 10 mg/h	7	376 mg	55 (14-349)/ 29 (6-200)	APACHE II score, 17 ± 4/18.2 ± 4
Marik, 1993[18]	Single center, RCT, South Africa	30 (14/16)	Severe CAP	Hydrocortisone	10 mg/kg/d	1	170 mg (set as 85 kg)	NA	APACHE II score, 11 ± 2/14 ± 6

All data are median (interquartile mean) or mean ± SD. APACHE = Acute Physiology and Chronic Health Evaluation Simplified Acute Physiology Score; CAP = community-acquired pneumonia; CRP = C-reactive protein; NA = not available; PSI = Pneumonia Severity Index score; RCT = randomized controlled trial; SAPS = Simplified acute physiology score.

mean Acute Physiology and Chronic Health Evaluation Simplified Acute Physiology Score II score of about 15 or the Pneumonia Severity Index score VI-V rate > 50%. Five included patients with mixed (mild to severe) CAP. In most studies, patients were administered corticosteroids for a short period (mean, about 7 days). After conversion to the equivalent dose of methylprednisolone, the mean dose was about 30 mg/d.

The characteristics of the six included cohort studies are shown in e-Table 1. All involved patients with severe CAP. The type of corticosteroids used in these studies varied, as did the length of use; the mean was about 7 days.

Primary Outcome

Nine trials with 1,667 randomized patients were included in the analysis of mortality. Figure 1 shows the pooled results from the random-effects model combining the relative risks (RRs). Corticosteroid treatment was not associated with a significant reduction in mortality (RR, 0.72; 95% CI, 0.43-1.21), with low heterogeneity among the studies ($I^2 = 27\%$). The absolute effect was 18 fewer per 1,000 (from 37 fewer to 14 more), and the GRADE quality was judged to be low, mainly because of inadequate sample size and high risk of bias (e-Table 2).

Five RCTs reported the effects of corticosteroids on mortality of patients with severe CAP. Use of corticosteroids did not significantly reduce mortality rates in these patients (347 patients with 35 events; RR, 0.72; 95% CI, 0.43-1.21), with no significant heterogeneity ($I^2 = 0\%$) (Fig 2). The GRADE quality was judged to be low (e-Table 2), and absolute effect was 48 fewer per 1,000 (from 91 fewer to 39 more). In the L'Abbé plot, with increased mortality in the placebo group, the mortality in the corticosteroids group increased slowly, which indicated a possible advantage of corticosteroids in the most patients with severe CAP (Fig 3). Trial sequential analysis found that the optimal sample size needed to reliably detect a plausible effect of treatment on the mortality of patients with severe CAP was 2,546 patients. The sequential monitoring boundary has not been crossed, indicating that the cumulative evidence is unreliable and inconclusive (Fig 4). Results from six observational studies that included 4,095 patients with severe CAP were pooled to confirm the results of RCTs. Treatment with corticosteroids for a short period did not significantly reduce the mortality rate in patients with severe CAP (RR, 1.00; 95% CI, 0.86-1.17), with heterogeneity being quite low ($I^2 = 0\%$).

TABLE 2] Efficacy Outcomes of Included RCTs

Study	Mortality	Length of Hospital Stay, d (Corticosteroids/ Control)	Length of ICU Stay, d (Corticosteroids/ Control)	Duration of IV Antibiotic Treatment, d (Corticosteroids/ Control)	Time to Clinical Stability, d (Corticosteroids/ Control)	Readmission to Hospital
Torres et al, 2015[4]	In-hospital mortality Corticosteroids (6/61) Control (9/59)	11 (7.5-14)/ 10.5 (8-15)	5 (3-8)/6 (4-8)	NA	4 (3-6)/5 (3-7)	NA
Blum et al, 2015[5]	All-cause mortality Corticosteroids (16/392) Control (13/393)	6 (6-7)/7 (7-8)	3 (2-4)/3 (1-12)	4 (3-6)/5 (3-7)	3.0 (2.5-3.4)/ 4.4 (4.0-5.0)	Corticosteroids (32/392) Control (28/ 393)
Nafae et al, 2013[13]	In-hospital mortality Corticosteroids (4/60) Control (6/20)	9.27 ± 2.4/ 16.5 ± 2.24	3.1 ± 4.9/6.3 ± 8.2	7.45 ± 2.6/13.9 ± 2.98	NA	NA
Meijvis et al, 2011[6]	In-hospital mortality Corticosteroids (8/151) Control (8/153)	6.5 (5.0-9.0)/ 7.5 (5.3-11.5)	21.5 (14.5-28.5)/ 15.5 (10.1-28.5)	5 ± 4.2/5.1 ± 3.5	NA	Corticosteroids (7/151) Control (7/153)
Fernández-Serrano et al, 2011[14]	Corticosteroids (1/28) Control (1/28)	10 (9-13)/12 (9-18)	6.5 (5.5-9.0)/ 10.5 (6.3-24.5)	NA	NA	NA
Snijders et al, 2010[15]	30-d mortality Corticosteroids (6/104) Control (6/109)	10.0 ± 12.0/ 10.6 ± 12.8	NA	NA	4.9 ± 6.8/4.9 ± 5.2	NA
Mikami et al, 2007[16]	Corticosteroids (1/15) Control (0/16)	11.3 ± 5.5/ 15.5 ± 10.7	NA	8.5 ± 3.2/12.3 ± 5.5	NA	NA
Confalonieri et al, 2005[17]	In-hospital mortality Corticosteroids (0/24) Control (7/24)	13 (10-53)/21 (3-72)	10 (4-33)/18 (3-45)	NA	NA	NA
Marik et al, 1993[18]	Corticosteroids (1/14) Control (3/16)	NA	4.3 ± 3.8/4.6 ± 5.9	NA	NA	NA

All data are median (interquartile mean) or mean ± SD. See Table 1 legend for expansion of abbreviations.

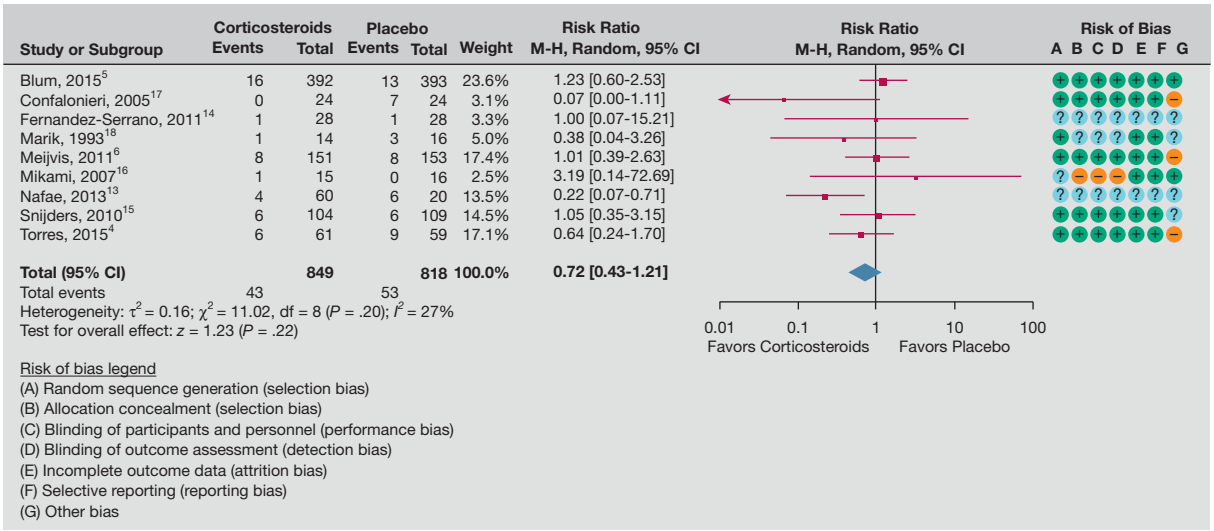

Figure 1 – *Mortality of patients with CAP according to treatment arm. The sizes of the squares denoting the point estimate in each study are proportional to the weight of the study. The diamonds represent the overall findings in each plot. For all study names, see the cited references. CAP = community-acquired pneumonia; M-H = Mantel-Haenszel.*

Secondary Outcomes

Because the data were reported inconsistently (data were shown as median [interquartile mean] or mean ± SD), we did not get a synthesized analysis of other efficacy outcomes. Although a pooled outcome was lacking, nearly all included studies show that corticosteroid treatment tended to reduce the lengths of hospital and ICU stays, the duration of IV antibiotic treatment, and the time to clinical stability (Table 2).

Corticosteroid administration was not associated with any adverse events, including hyperglycemia, superinfection, GI bleeding, and empyema. The GRADE quality was judged to range from very low to low. Corticosteroid treatment was associated,

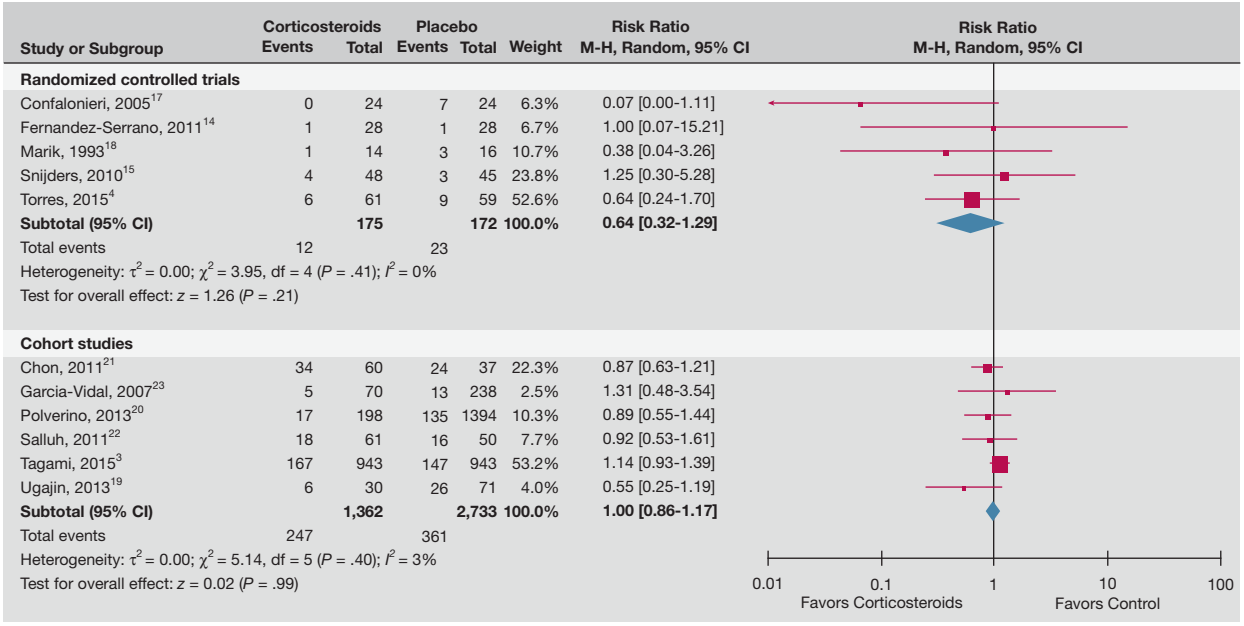

Figure 2 – *Mortality of patients with severe CAP according to treatment arm. The sizes of the squares denoting the point estimate in each study are proportional to the weight of the study. The diamonds represent the overall findings in each plot. For all study name acronyms, see the cited references. See Figure 1 legend for expansion of abbreviations.*

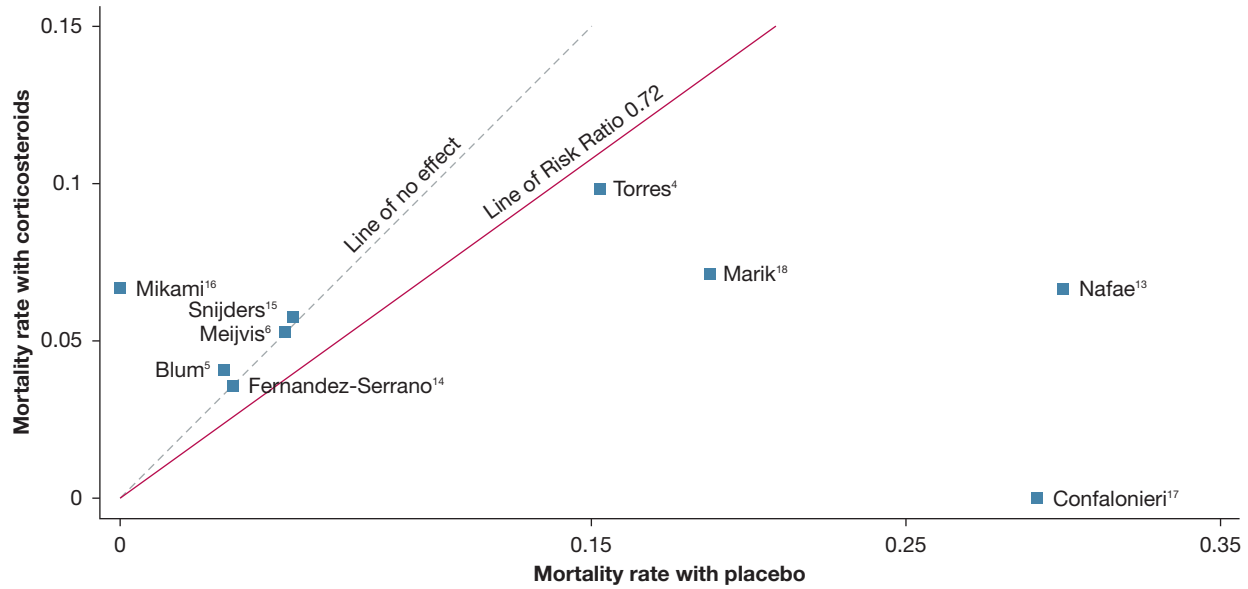

Figure 3 – *L'Abbe plot according to treatment arm. The nine trials of corticosteroids and CAP are presented in a L'Abbe plot. With the increase of mortality in the placebo group, the mortality in the corticosteroids group increased slowly, which indicated possible advantage of corticosteroids in most patients with severe CAP. See Figure 1 legend for expansion of abbreviations.*

however, with a decreased risk of ARDS (RR, 0.21; 95% CI, 0.08-0.59). This index was not prespecified in the included studies, and the result was dominated by an unclear bias study,[13] so it should be interpreted with caution (e-Figure 2).

Risk of Bias and Subgroup Analyses

The risk of bias relative to reports of mortality is shown e-Figure 3A. The selection and attrition biases were well-controlled in most studies. However, imbalances were reported in patients with septic shock,[4] severe CAP,[6] and high levels of inflammation,[15] and one trial was terminated early.[17] The risk of bias relative to adverse events is shown in e-Figure 3B. Five studies were judged to be of high quality. Three were judged to be of fair quality, mainly because adverse events were not prespecified and the ascertainment technique was not adequately described.

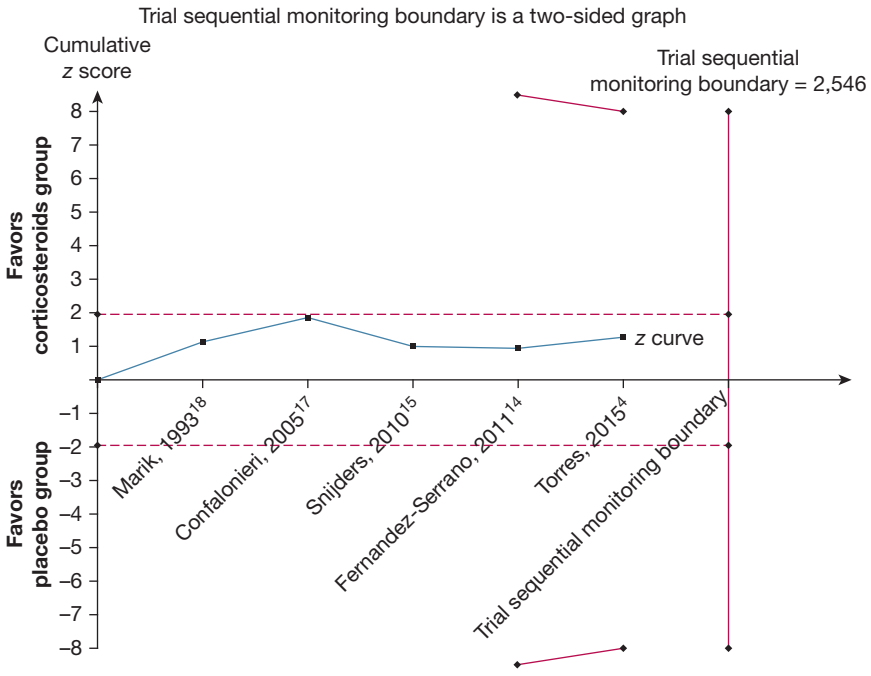

Figure 4 – *Trial sequential analysis of studies with patients with severe CAP. Trial sequential analysis, assuming a 15% mortality rate in the control group and a 25% relative risk reduction with 80% power and a two-sided α of 0.01, found that the optimal sample size needed to reliably detect a plausible effect of treatment on the mortality of patients with severe CAP was 2,546 patients. The sequential monitoring boundary has not been crossed, indicating that the cumulative evidence is unreliable and inconclusive. See Figure 1 legend for expansion of abbreviations.*

TABLE 3] Subgroup Analysis of Mortality in RCTs

Stratification	No. of Patients (Studies)	No. of Events/No. in Group (%)		RR (95% CI)	*P* Value	I^2, %
		Corticosteroids	Placebo			
Subgroup analysis						
Effects model						
M-H random-effects model	1,667 (9)	43/849 (5.1)	53/818 (6.4)	0.72 (0.43-1.21)	.22	27
M-H fixed effects model	1,667 (9)	43/849 (5.1)	53/818 (6.4)	0.74 (0.51-1.09)	.13	27
Severity of CAP						
Severe CAP	347 (5)	12/175 (6.8)	23/172 (13.4)	0.64 (0.32-1.29)	.21	0
Mixed CAP	1,413 (5)	35/722 (4.8)	33/691 (4.8)	0.84 (0.43-1.65)	.62	44
Inflammatory response						
High CRP (> 250 mg/dL)	381 (3)	12/189 (6.3)	22/192 (11.4)	0.61 (0.21-1.72)	.35	44
Low CRP (≤ 250 mg/dL)	1,120 (3)	25/558 (4.5)	21/562 (3.7)	1.19 (0.68-2.09)	.55	0
Use of loading dose						
Yes	184 (3)	5/112 (4.5)	14/72 (19.4)	0.23 (0.09-0.63)	.004	0
No	1,483 (6)	38/737 (5.2)	39/746 (5.2)	0.98 (0.63-1.52)	.93	0
Effective pharmacological effect reached						
Yes	608 (5)	19/324 (5.9)	31/284 (10.9)	0.5 (0.23-1.10)	.08	38
No	1,059 (4)	24/525 (4.6)	22/534 (4.1)	1.12 (0.63-1.98)	.69	0
Duration of corticosteroid treatment						
≥ 7 d	1,182 (5)	27/608 (4.4)	33/574 (5.7)	0.59 (0.23-1.51)	.27	57
< 7 d	485 (4)	16/241 (6.6)	20/244 (8.2)	0.80 (0.43-1.52)	.5	0
Cumulative dose of corticosteroids						
> 300 mg	304 (4)	11/173 (6.4)	23/131 (17.6)	0.37 (0.15-0.90)	.03	25
≤ 300 mg	1,363 (5)	32/676 (4.7)	30/687 (4.4)	1.09 (0.67-1.78)	.72	0
Type of mortality						
In-hospital mortality	552 (4)	18/296 (6.1)	30/256 (11.7)	0.46 (0.19-1.12)	.10	52
Mortality without explanation	902 (4)	19/449 (4.2)	17/453 (3.7)	1.14 (0.60-2.18)	.69	0
30-day mortality	213 (1)	6/104 (5.8)	6/109 (5.5)	1.05 (0.35-3.15)	.93	…
Sensitivity analysis						
Multicenter	1,257 (4)	30/628 (4.7)	37/629 (5.9)	0.84 (0.43-1.63)	.6	37
Large sample (> 100)	1,422 (4)	36/708 (5.1)	36/714 (5.0)	1.0 (0.64-1.57)	1.0	0
Low risk of bias	1,500 (6)	37/746 (5.0)	46/754 (6.1)	0.88 (0.55-1.41)	.6	8
One-study-out method	…	…	…	From 0.62 (0.35-1.09) to 0.92 (0.60-1.41)	…	…

M-H = Mantel-Haenszel; RR= relative risk. See Table 1 legend for expansion of other abbreviations.

Most subgroups showed no significant differences in mortality of patients with CAP (Table 3). However, pooling of data from three studies in which patients were administered a loading dose of corticosteroids[13,14,17] showed that corticosteroid treatment improved mortality (RR, 0.23; 95% CI, 0.09-0.63); a cumulative dose of corticosteroids > 300 mg in four studies involving 304 patients was associated with a significant reduction in mortality rate (RR, 0.37; 95% CI, 0.15-0.90).[4,13,14,17] These subgroup results should be interpreted with caution because of the limited sample size and the potential bias inherent to subgroup analysis.

The findings of the meta-analysis remained stable with only multicenter, low risk of bias, or large sample studies. In addition, exclusion of the results of any single study did not alter the overall findings of the analysis. Funnel plots showed no evidence of publication bias (e-Figure 4).

Discussion

This systematic review and meta-analysis identified nine RCTs and six observational studies investigating the effect of corticosteroids on mortality in patients with CAP or severe CAP. The analysis found that treatment with corticosteroids was not associated with a significant reduction in mortality rate, regardless of high or low inflammatory response and short- or long-term corticosteroid treatment. But corticosteroid treatment was associated with a decreased risk of ARDS and may reduce lengths of hospital and ICU stays, duration of IV antibiotic treatment, and time to clinical stability.

Several large multicenter RCTs assessed the effects of corticosteroids in patients with CAP.[4-6] These trials did not assess the effects of corticosteroids on patient mortality because of their low sample size. Although a meta-analysis[7] found that corticosteroid use was associated with reduced mortality in patients with severe CAP, that analysis was based on four studies with 214 patients, and the study[26] with the greatest weight had a high risk of bias. In addition, 8-day mortality was reported in this study[26]; allowing for that, other included mortality data were 30-day mortality or in-hospital mortality, and the mean time to death of patients with CAP was 9 days.[5] It may be inappropriate to be included in the overall analyses. More recently, a meta-analysis by Siemieniuk et al[27] found that adjunctive corticosteroids were associated with possible reductions in all-cause mortality, especially in patients with severe CAP. They also found that adjunctive corticosteroids increased frequency of hyperglycemia requiring treatment. By contrast, the meta-analysis presented in this study, which included five RCTs of patients with severe CAP, found that corticosteroid treatment was not associated with a reduction in mortality rate. This result was confirmed by pooling with six observational studies, involving 608 events in 4,095 patients, adding robustness to the main findings.

In the study by Siemieniuk et al,[27] two old studies,[24,25] completed in 1956 and 1972, were included, but excluded in our study. The type and principles of antibiotic use and other medical procedures during those times differed markedly from present medical protocols. The definition of CAP was not clear in these studies. Additionally, the lengths of hospital and ICU stays, the duration of IV antibiotic treatment, and the time to clinical stability in five included studies[4-6,14,17] were shown as medians with interquartile ranges. All of these studies stated their data were substantially skewed distributions. Pooled, the converted data were not recommended by the Cochrane Collaboration, and the result may be misleading. In the meta-analysis by Siemieniuk et al[27], the continuous variable data were converted and pooled. Though various sensitivity analyses were used to avoid the possible bias, the pooled results had a high degree of heterogeneity and may lead to a misleading conclusion. To reduce the possible bias resulting from data conversion, we only get qualitative descriptions with estimations; our results may be more believable.

The finding that corticosteroids were not associated with a survival advantage may have been due to the corticosteroid dose being insufficient to achieve an effective serum concentration over 24 h.[6] For example, in one study, patients were administered a single dose of 40 mg/d prednisolone for 7 days because of the short biological half-life, resulting in serum concentrations and pharmacological effects that were ineffective.[15] This was tested in a subgroup analysis of studies in which patients achieved effective serum concentrations; although corticosteroids tended to reduce mortality rates, the difference was not statistically significant. Corticosteroids may modulate cytokine release, such that patients with severe CAP and a high inflammatory response would be more likely to benefit from corticosteroid treatment.[4] The study by Torres et al[4] showed a decreased treatment failure rate of about 18% in patients with high inflammatory response. Subgroup analysis of patients with mean C-reactive protein concentration $>$ 250 mg/L found no significant reduction in mortality rate.

Another explanation for the lack of corticosteroid effect on patient mortality was that these agents were associated with a rebound of inflammatory responses after their use was halted. Two studies[6,15] found an apparent rebound effect of C-reactive protein concentrations by about day 10. In addition, large doses of corticosteroids or their use for more than 7 days may be associated with side effects. Our subgroup analysis, however, did not find an association between mortality and period of treatment ($<$ 7 vs $\geq$ 7 days).

This systematic review has limitations. First, the number of patients with severe CAP was small, suggesting that the result may not be stabilized. Nevertheless, the robustness of our conclusions was supported by our use of Cochrane risk of bias assessment leading to GRADE evaluations, by our trial sequential analysis, and by

pooling observational studies. Second, the severity of illness was not consistent across the studies. There was substantial variation in mortality across the control groups (< 10% to > 30%) in patients with severe CAP, which may due to the lack of uniform diagnostic criteria of severe CAP. To explore the relationship between severity of illness and response to intervention, we drew a L'Abbé plot and found a possible advantage of corticosteroids in most patients with severe CAP. Third, the hypothesis that corticosteroids improved mortality was not confirmed in this study. This hypothesis may have been based on biases resulting from imbalances of patients with septic shock, COPD, or asthma. Most studies did not report related data, emphasizing the need for additional studies.

Conclusions

The present systematic review and meta-analysis indicate that corticosteroid treatment is safe and may reduce the risk of ARDS, the lengths of hospital and ICU stays, the duration of IV antibiotic treatment, and the time to clinical stability. Our study suggests that corticosteroid treatment is not associated with decreased mortality rates in patients with CAP or severe CAP, but the trial sequential analysis indicate more studies are needed to confirm this result.

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Additional information: The e-Appendixes, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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