

Adjuvant Steroid Therapy in Community-Acquired Pneumonia: A Systematic Review and Meta-analysis

Majid Shafiq, MD^{1*}, Muhammad S. Mansoor, MD², Adnan A. Khan, MD¹, M. Rizwan Sohail, MD³, Mohammad H. Murad, MD, MPH²

¹Division of Hospital Internal Medicine, ²The Knowledge and Evaluation Research Unit, ³Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota.

BACKGROUND: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality among adults. Although steroids appear to be beneficial in animal models of CAP, clinical trial data in humans are either equivocal or conflicting.

PURPOSE: Our purpose was to perform a systematic review and meta-analysis of studies examining the impact of steroid therapy on clinical outcomes among adults admitted with CAP.

DATA SOURCES AND STUDY SELECTION: We identified randomized controlled trials (RCTs) through a systematic search of published literature up to July 2011.

DATA EXTRACTION: We estimated relative risks (RR) and weighted mean differences, pooled from each study using a random effects model.

DATA SYNTHESIS: Eight RCTs, comprising 1119 patients, met our selection criteria. Overall quality of the studies was moderate. Adjunctive steroid therapy had no effect on hospital mortality or length of stay in the intensive care unit, but reduced the overall length of hospital stay (RR: −1.21 days [95% confidence interval (CI): −2.12 to −0.29]). Less robust data also demonstrated reduced incidence of delayed shock (RR: 0.12 [95% CI: 0.03 to 0.41]) and reduced persistence of chest x-ray abnormalities (RR: 0.13 [95% CI: 0.06 to 0.27]). A priori subgroup and sensitivity analyses did not alter these findings.

CONCLUSIONS: Moderate-quality evidence suggests that adjunctive steroid therapy for adults hospitalized with CAP reduced the length of hospital stay but did not alter mortality. *Journal of Hospital Medicine* 2013;8:68–75. © 2012 Society of Hospital Medicine

Community-acquired pneumonia (CAP) is the most common lower respiratory tract infection in adults and a leading cause of infection-related deaths in the United States.¹ According to a survey, pneumonia was the most common reason for hospital admissions through the emergency department in 2003.² CAP is associated with significant morbidity and mortality among those sick enough to require hospitalization. In a prospective study, hospital mortality rates ranged from 5% to 18% and length of stay from 9 to 23 days depending on patient location (intensive care unit [ICU] vs elsewhere) and severity of illness.³

Empirical evidence suggests that host inflammatory response contributes significantly to lung injury in pneumonia.⁴ Studies have demonstrated reduction in the host inflammatory response as well as in mortality among animals with bacterial pneumonia when exposed to glucocorticoids.^{5,6} Furthermore, the

efficacy of adjunctive steroid therapy in severe pneumonia caused by *Pneumocystis jirovecii*⁷ and in pneumococcal meningitis^{8,9} is already established. However, due to equivocal, and at times conflicting, human clinical trial data on the impact of steroid therapy in CAP, the 2007 consensus guidelines (jointly published by the Infectious Diseases Society of America and American Thoracic Society) do not provide recommendations for or against use of steroids in CAP, except in the setting of hypotension secondary to adrenal insufficiency.¹⁰

In their meta-analysis, Chen et al. analyzed data from 6 randomized clinical trials (RCTs) published between 1972 and 2007 (including 2 on pediatric patients) and concluded that adding steroids to current standard of care was not beneficial.¹¹ Earlier, Lamontagne et al.'s meta-analysis included RCTs on hospitalized CAP patients as well as those on patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) from any cause.¹² They concluded that low-dose corticosteroid therapy reduced all-cause in-hospital mortality in this mixed patient population (relative risk [RR]: 0.68 [95% confidence interval (CI): 0.49 to 0.96]). Recently, data from a number of additional RCTs have become available.^{13–17} Therefore, an updated review of RCTs evaluating the role of adjunctive steroid therapy among adults hospitalized with CAP was warranted.

*Address for correspondence and reprint requests: Majid Shafiq, MD, Division of General Internal Medicine — Johns Hopkins Hospital, 600 N. Wolfe St, Nelson 215, Baltimore, MD 21287; Telephone: 443-287-3631; Fax: 410-502-0923; E-mail: mshafiq1@jhmi.edu

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MATERIALS AND METHODS

We conducted this systematic review and meta-analysis in accordance with the recommendations published in the *Cochrane Handbook for Systematic Reviews of Interventions*¹⁸ and reported our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.¹⁹ The overall quality of evidence was judged using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.²⁰

Data Sources and Search Strategies

A comprehensive search of several databases including PubMed, Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials, and Scopus was conducted. The time range for search started from each database's earliest inclusive dates up to July 2011. An experienced institutional librarian assisted with the design and conduct of our literature search. Controlled vocabulary, supplemented with keywords, was used to search for the topic: steroid therapy for community-acquired pneumonia. We consulted expert colleagues to ensure the inclusion of all eligible reports and also checked the bibliographies of previously published systematic reviews.^{11,21}

Eligibility Criteria

Studies deemed eligible for inclusion were RCTs that met the following patients, intervention, control, outcomes (PICO) criteria: P, adults hospitalized with CAP; I, administration of systemic corticosteroids plus standard treatment; C, standard treatment without corticosteroids; O, primary outcome: hospital mortality; secondary outcomes, length of hospital stay, length of ICU stay and duration of mechanical ventilation. Under the P criterion we included RCTs that defined CAP as a lung infection (based on a reasonable combination of history, physical examination, imaging, and/or other investigative data, such as per the American Thoracic Society definition)²² of presumed or proven bacterial etiology, in a patient who was not immunocompromised and had no exposure to a healthcare facility in the past 90 days.

Study Selection and Quality Assessment

Two reviewers independently performed study selection, data extraction, and quality assessment. Data were abstracted using standardized data collection instruments. Kappa statistic was calculated to assess the reviewers' level of agreement.

We perused full texts of all articles whose abstracts met selection criteria, performing an appraisal of their quality using the Cochrane risk-of-bias tool.²³ We also reviewed the baseline characteristics of patients in each study cohort.

Analysis

We estimated RR and weighted mean differences along with the respective 95% confidence intervals by pooling data using a random effects model.²⁴ Study heterogeneity was assessed using the I^2 statistic, which estimates the percentage of variation that is not attributable to chance.²⁵ We performed a priori subgroup analyses based on the location (ICU vs non-ICU) and mean age group of study participants (based on a cutoff of 50 years). A significant ($P < 0.05$) test of interaction would provide an explanation for any heterogeneity.²⁶ We also performed an a priori sensitivity analysis excluding any studies published before the year 2000 to exclude the impact of changing standards of care for inpatient management of CAP over time.

The original investigators were not contacted for purposes of obtaining raw data.

RESULTS

Eight RCTs, comprising 1119 subjects, were eventually chosen.^{13–16,27–30} Seven shortlisted studies were excluded due to methodological limitations, failure to fully meet PICO criteria, or gross insufficiency of descriptive data on subjects or methodology.^{17,31–36} Figure 1 illustrates the study selection process.

Table 1 summarizes the baseline characteristics of patient populations from each study. Mean ages in 7 RCTs were between 60 years and 80 years. In Marik et al., the mean age of the intervention group was 31.7 years, whereas that of the control group was 40.6 years (P value not reported).²⁹ Three RCTs included ICU patients only,^{16,27,29} whereas 4 only included general medical ward patients.^{13,14,28,30} Disease severity scores at admission were similar between the 2 groups in all RCTs except Sabry and Omar,¹⁶ which was the only clinical trial to use a chest radiograph score. Only Sabry and Omar,¹⁶ and Mikami et al.²⁸ excluded chronic obstructive pulmonary disease patients. Where possible, the serum C-reactive protein (CRP) value on day one was subtracted from that on day eight to generate a one week "delta CRP."

The mean ICU length of stay was 12.7 days for the steroid group and 12.3 days for the control group. The mean hospital lengths of stay were 10.2 days and 13.6 days, respectively. Quality of the studies was moderate (see Supporting Information, Appendix I, in the online version of this article). Kappa score was >0.90 .

Meta-analysis

Figure 2 illustrates the results of our meta-analyses. Although adjunctive steroid therapy had no effect on hospital mortality or ICU length of stay, it was associated with reduced hospital length of stay (RR: -1.21 days [95% CI: -2.12 to -0.29]). Of note, Mikami et al.²⁸ did not report mortality in their article, whereas in McHardy and Schonell,³⁰ using the factorial design, each of the 2 treatment groups were

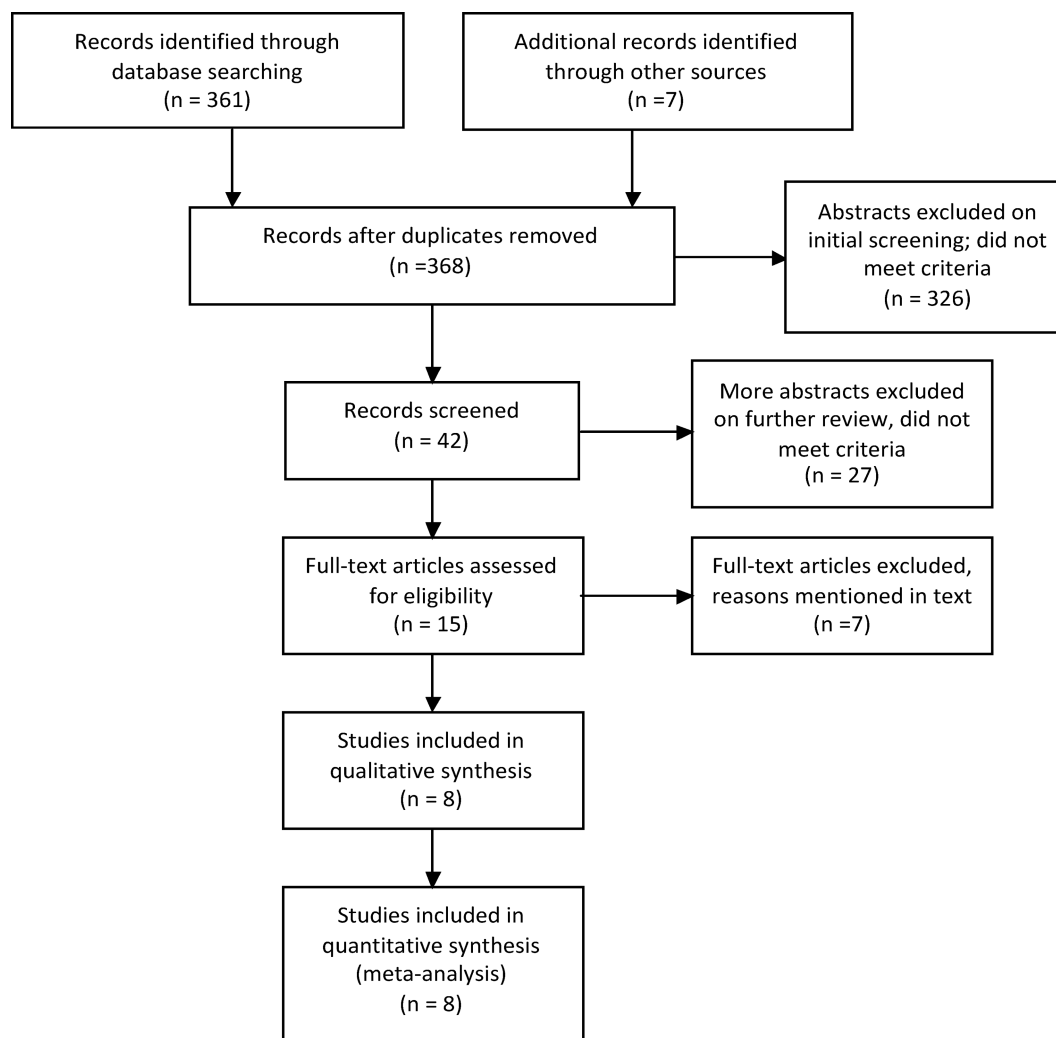


FIG. 1. The study selection process.

further subdivided into those patients who received 1 g of ampicillin and those who received 2 g of ampicillin (Figure 2A).

Analysis of other outcomes was limited by the fact that data were pooled from only a few studies. These included the need for and duration of mechanical ventilation, development of new ARDS and ICU admission rate, neither of which was associated with steroid therapy. However, steroid use was associated with lower incidence of delayed shock (ie, shock occurring after enrollment (RR: 0.12 [95% CI: 0.03 to 0.41]) and lower incidence of persistent chest x-ray abnormalities at 1 week (RR: 0.13 [95% CI: 0.06 to 0.27]).

Subgroup and Sensitivity Analyses

Heterogeneity (I^2 statistic) was <50% for all outcomes except ICU length of stay (74%). There were no significant interactions to suggest a subgroup effect based on older vs younger or ICU vs non-ICU based patients (Table 2). In a priori sensitivity analysis that excluded McHardy and Schonell (published in 1972) and Marik et al. (published in 1993),²⁹ the results were not different from the main analysis.

Quality of Evidence

Using the GRADE framework, the overall quality of evidence (confidence in the estimates) was judged to be moderate with the following main limitations: 1) methodological limitations among included studies (prognostic imbalance), 2) imprecision (small number of events and wide confidence intervals), and 3) inconsistency in the outcome ICU length of stay (as reflected by the I^2 statistic).

Other Reported Outcomes

Four studies^{14,15,28,30} provided descriptive details of microbiologic data, whereas 1 study¹⁵ provided analytical data on microbiology. In the latter, patients with *Streptococcus pneumoniae* infection (identified variably by sputum, pleural fluid, urine, or blood samples), had lower clinical cure rates in the steroid group at day 30 ($P = 0.01$) and higher numbers of late failures (defined as recurrence of signs and symptoms of pneumonia, $P = 0.02$).

Three^{27,29,30} studies did not provide data on glycemic trends, whereas Fernandez-Serrano et al., Mikami et al., and Snijders et al. reported that rates of hyperglycemia were not different across the 2 groups.^{14,15,28}

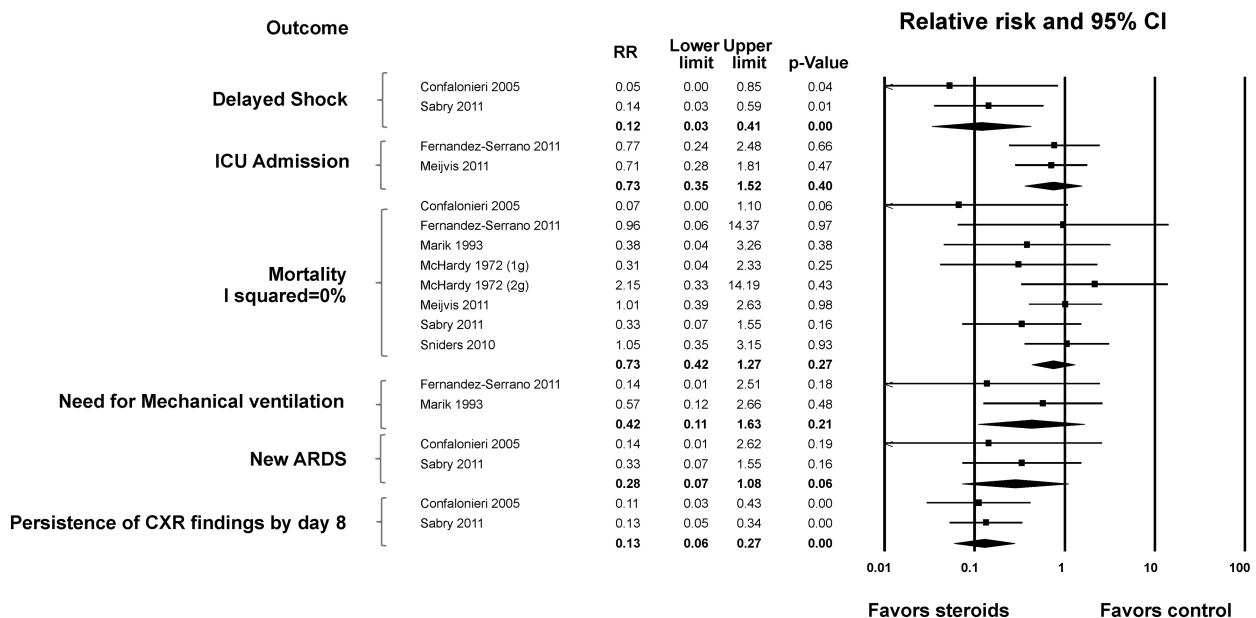
TABLE 1. Baseline Characteristics of Studies Included for Analysis

Author, Year	Number of Patients		Gender, Males (% Age)		Age (y)		Steroids Used (Daily Dose and Duration)		COPD (% of Total)		Diabetes (% of Total)		Mean PaO ₂ /FIO ₂ Ratio		Severity Score (Score: Mean)		Patients Already in ICU (% of Total)		One-week Delta CRP (mg/dL)	
	Total	Steroid	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control	Steroid	Control
McHardy 1972 ³¹	126	40	86	45	50	62	59	Prednisolone 20 mg, 7 d	40	35	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	0	0	N/A	N/A
Marik 1993 ³⁰	30	14	16	Not reported		32	41	Hydrocortisone 10 mg/kg × 1	Not reported	Not reported	Not reported	Not reported	213	214	APACHE II	100	100	N/A	N/A	
Confalonieri 2005 ²⁸	46	23	23	74	65	60	67	Hydrocortisone 200 mg bolus, then 10 mg/h, 7 d	Not reported	Not reported	Not reported	Not reported	141*	178*	APACHE II	100	100	-37*	+5*	
Mikami 2007 ²⁹	31	15	16	73.3	75	76	68	Prednisolone 40 mg IV, 3 d	0	0	Not reported	Not reported	PaO ₂ (FIO ₂ not reported)	61	64	PSI	0	0	N/A	N/A
Snijders 2010 ¹⁶	213	104	109	52.9	63.3	63	64	Prednisolone 40 mg IV/PO, 7 d	18	22	10	11	Not reported	Not reported	95	86	14.4	6.4	N/A	N/A
Fernandez-Serrano 2011 ¹⁵	45	23	22	69.6	63.6	66	61	Methylprednisolone 200 mg IV; then 20 mg/6 h, 3 d; then 20 mg/12 h, 3 d; then 20 mg/d, 3 d	17	9	9	18	200	257	PSI class V (% of total)	13	0	0	N/A	N/A
															65	54				
Meijvis 2011 ¹⁴	304	151	153	57	56	65	63	Dexamethasone 5 mg/d, 4 d	13	9	15	14	Not reported	Not reported	PSI class V (% of total)	17	0	0	N/A	N/A
Sabry 2011 ¹⁷	80	40	40	30	28	62	63	Hydrocortisone 200 mg IV, then 12.5 mg/h, 7 d	0	0	Not reported	Not reported	338*	243*	Chest radiograph score	1*	100	100	-38*	-23*
															3*	3*				

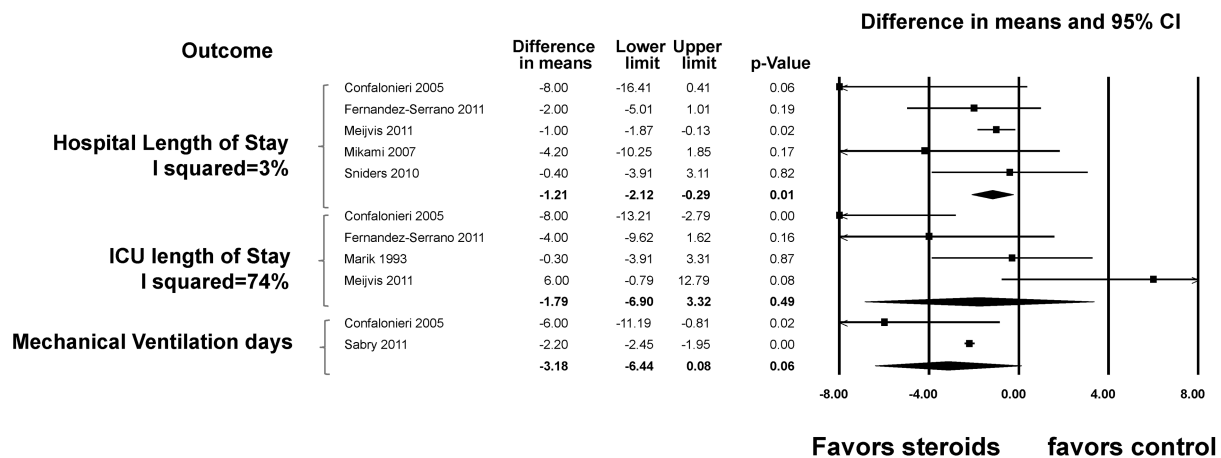
NOTE: Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; IV, intravenous; NA, not applicable; PO, orally; PSI = Pneumonia Severity Index; SAPS, Simplified Acute Physiology Score. The difference between steroid and control groups was statistically significant (P<0.05).

NOTE: Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; IV, intravenous; NA, not applicable; PO, orally; PSI = Pneumonia Severity Index; SAPS, Simplified Acute Physiology Score.

*The difference between steroid and control groups was statistically significant (P<0.05)



Meta Analysis



Meta Analysis

FIG. 2. (A) Meta-analysis of the dichotomous outcomes. (B) Meta-analysis of the continuous outcomes. Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; CXR, chest radiograph; ICU, intensive care unit; RR, relative risk.

Meijvis et al.¹³ reported more frequent hyperglycemia in the steroid group (44% vs 23%, $P < 0.001$) but no difference in the need for glucose-lowering treatment (5% vs 3%, $P = 0.57$). Sabry and Omar¹⁶ reported a higher incidence of hyperglycemia in the steroid group (no numerical data reported). Snijders et al.,¹⁵ Meijvis et al.,¹³ and Sabry and Omar¹⁶ reported that the rates of super-infection were not different between the 2 groups. No other adverse effects were consistently reported.

DISCUSSION

In this meta-analysis of 8 RCTs, we found no significant association between steroid therapy and our

primary outcome of interest (hospital mortality). However, length of hospital stay was shorter in the steroid group. These findings were not altered in various sensitivity and subgroup analyses. Although adverse effects of steroid therapy were not consistently reported, most of the RCTs reported that hyperglycemia was either no more common in the steroid group or did not require additional treatment.

Previous meta-analyses have also concluded that adding corticosteroids to conventional therapy does not impact mortality among adults hospitalized with CAP.^{11,21} This may or may not be a consequence of inadequate statistical power. Although Lamontagne et al.¹² reported that low-dose corticosteroid therapy

TABLE 2. Subgroup Analyses

	No. of Studies	Effect Size	LL	UL	P for Interaction (Difference Between Subgroups)
Mortality					
ICU	3	0.27	0.08	0.83	0.06
Non-ICU	4	0.96	0.45	2.05	
Older	7	0.75	0.40	1.38	0.56
Young	1	0.38	0.04	3.26	
Need for mechanical ventilation					
ICU	1	0.57	0.12	2.66	0.39
Non-ICU	1	0.14	0.01	2.51	
Older	1	0.14	0.01	2.51	0.39
Younger	1	0.57	0.12	2.66	
LOS					
ICU	1	-8.00	-16.41	0.41	0.11
Non-ICU	3	-1.14	-1.97	-0.31	
ICU LOS					
ICU	2	-3.91	-11.44	3.62	0.45
Non-ICU	2	0.81	-8.98	10.60	
Older	3	-2.26	-9.95	5.43	0.65
Younger	1	-0.30	-3.91	3.31	

NOTE: Abbreviations: ICU, intensive care unit; LOS, length of stay; LL, Lower Limit; UL, Upper Limit.

(2 mg/kg/day or less of methylprednisolone or equivalent) was associated with reduced hospital mortality (RR: 0.68 [95% CI: 0.49 to 0.96]), this result was obtained by pooling data from 5 RCTs on adults hospitalized with CAP and 4 on adults with ALI/ARDS from any cause. In a subgroup analysis of RCTs conducted only on CAP patients, no impact on mortality was found. Of note, all RCTs involving CAP patients had used low-dose steroids; the 3 RCTs using high-dose steroids were carried out on ALI/ARDS patients.^{36–38} Similarly, all RCTs in our meta-analysis were also characterized by steroid doses under 2 mg/kg/day of methylprednisolone or equivalent.

Our study is the first to demonstrate decreased length of hospital stay in this patient population. Importantly, each of the 5 studies that reported this outcome (including 3 relatively recent RCTs) showed the same trend. However, it is not inconceivable that steroid use led to a quicker decline in cytokine levels resulting in an earlier resolution of fever and hence earlier discharge without a faster cure per se. The two studies whose data permitted calculation of delta CRP also demonstrated a faster CRP decline in the steroid group (Table 1).

Our analysis also suggested reduced incidence of delayed shock. However, these data were pooled from only 2 RCTs,^{16,27} and each of them used hydrocortisone, whose direct mineralocorticoid effect is an obvious confounder. Similarly, according to data pooled from 2 RCTs, steroid use was associated with fewer cases of persistent chest x-ray abnormalities by day 8. Of note, although calculation of the I^2 statistic was not possible because of too few studies, visual inspection of the forest plots suggested low levels of heterogeneity.

It is plausible that the impact of adjunctive steroids in CAP may vary based on the causative pathogen.

This pathogen-specific association has been observed in patients with bacterial meningitis, where most of the benefit is seemingly limited to pneumococcal meningitis.^{8,9} Unfortunately, as demonstrated by Snijders et al.,¹⁵ establishing microbiologic etiology in CAP can be difficult, and most patients are treated empirically.

Our analysis showed no difference in duration of ventilation among patients who required ventilatory support on admission. However, only 2 studies reported this outcome.^{16,27} Second, in Confalonieri et al.,²⁷ the steroid group had a more severe baseline inflammatory response as illustrated by higher serum CRP levels ($P = 0.04$). Moreover, while mechanical ventilation was defined as either invasive or noninvasive ventilation, the steroid group had a higher number of patients who required noninvasive ventilation ($P = 0.03$), thus introducing selection bias. This study had additional areas of concern too, including a mortality of 0 among its 46 ICU patients, in contrast to established mortality rates of up to around 20%.³ Unlike this study, Sabry and Omar¹⁶ reported that none of their patients was on noninvasive ventilation. It may be pertinent to compare our findings with those of Steinberg et al.,³⁹ who studied patients with ARDS (pneumonia being the most common cause) who received methylprednisolone. This group had an early increase in ventilator-free days, but that effect became less pronounced (though still significant) when the study end point was prolonged from 30 to 90 days.⁴⁰

The 2 studies that were published before 2000 (McHardy and Schonell,³⁰ and Marik et al.²⁹) were excluded in our a priori sensitivity analysis. A number of considerations led to this decision. First, standards of care for inpatient management of pneumonia—including pharmacologic therapies and ventilation strategies—have changed considerably over time. For instance, newer generation macrolides became available for clinical use in the early 1990s and meropenem in 1996.⁴¹ Therefore, it would be hard to assume constancy of effect from that time period. Furthermore, the study by McHardy and Schonell³⁰ suffered from significant differences in the baseline characteristics of its 2 arms. There was incomplete randomization; patients with diabetes were excluded from only the steroid arm. Another issue with Marik et al.²⁹ was the considerably younger age of participants compared to other studies (Table 1).

Limitations

In spite of our relatively stringent selection criteria and a number of subgroup and sensitivity analyses, the overall quality of evidence was only moderate (Table 2). Key issues with the findings reported by Confalonieri et al.,²⁷ McHardy and Schonell,³⁰ and Marik et al.³⁰ were discussed earlier. Baseline severity of illness, patient comorbidities, and length of follow-

up were variable both within and across various studies. Another major limitation was that the intervention of interest (ie, steroid therapy) was not uniformly applied as the regimens varied considerably even though all regimens fit the designation of low-dose steroids as previously noted (Table 1).

In conclusion, although evidence suggests that adjunctive steroid therapy is associated with reduced hospital length of stay, the data are not strong enough to recommend routine use of steroids among all adults hospitalized with CAP. However, considering that there was no increase in mortality or hospital length of stay with steroid use, it is reasonable to continue steroids if warranted for treatment of underlying comorbid conditions.

Due to the aforementioned limitations in RCTs published to date, we believe that additional studies that are more robustly designed and sufficiently powered to detect differences in key outcomes (including mortality) are warranted. Investigators should ensure appropriate randomization of groups, taking into account severity of illness, comorbid conditions and prior use of steroid therapy. Standardizing the intervention (including dose and duration of steroid therapy and time to first antibiotic dose) would be essential. Concurrent measurement of inflammatory markers such as delta CRP would be useful too. Finally, accurate measurement of all secondary outcomes of interest, including adverse effects and duration of both invasive and noninvasive mechanical ventilation, would be important to accurately study the benefit of steroids among the most likely beneficiaries: those patients who are the sickest.

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