Annals of Internal Medicine REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

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Background: Community-acquired pneumonia (CAP) is common and often severe.

Purpose: To examine the effect of adjunctive corticosteroid therapy on mortality, morbidity, and duration of hospitalization in patients with CAP.

Data Sources: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials through 24 May 2015.

Study Selection: Randomized trials of systemic corticosteroids in hospitalized adults with CAP.

Data Extraction: Two reviewers independently extracted study data and assessed risk of bias. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation system by consensus among the authors.

Data Synthesis: The median age was typically in the 60s, and approximately 60% of patients were male. Adjunctive corticosteroids were associated with possible reductions in all-cause mortality (12 trials; 1974 patients; risk ratio [RR], 0.67 [95% CI, 0.45 to 1.01]; risk difference [RD], 2.8%; moderate certainty), need for mechanical ventilation (5 trials; 1060 patients; RR, 0.45 [CI, 0.26 to 0.79]; RD, 5.0%; moderate certainty), and the acute respiratory distress syndrome (4 trials; 945 patients; RR, 0.24 [CI, 0.10 to 0.56]; RD, 6.2%; moderate certainty). They also decreased time to clinical stability (5 trials; 1180 patients; mean difference, −1.22 days [CI, −2.08 to −0.35 days]; high certainty) and duration of hospitalization (6 trials; 1499 patients; mean difference, −1.00 day [CI, −1.79 to −0.21 days]; high certainty). Adjunctive corticosteroids increased frequency of hyperglycemia requiring treatment (6 trials; 1534 patients; RR, 1.49 [CI, 1.01 to 2.19]; RD, 3.5%; high certainty) but did not increase frequency of gastrointestinal hemorrhage.

Limitations: There were few events and trials for many outcomes. Trials often excluded patients at high risk for adverse events.

Conclusion: For hospitalized adults with CAP, systemic corticosteroid therapy may reduce mortality by approximately 3%, need for mechanical ventilation by approximately 5%, and hospital stay by approximately 1 day.

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Lower respiratory infections are the second most common cause of life-years lost globally (1). In developed countries, hospitalization for community-acquired pneumonia (CAP) is common, is often associated with the acute respiratory distress syndrome (ARDS) requiring mechanical ventilation (2), and is associated with appreciable mortality (3). Hospitalizations for CAP cost more than €10 billion annually in Europe (4) and more than $10 billion annually in the United States (3).

Pneumonia occurs when components of the innate immune system fail to clear a pathogen from the lower respiratory tract (5). Although local and cytokine-mediated systematic inflammatory responses may help clear bacterial pathogens, they may also cause harm. Local inflammation exacerbates pulmonary dysfunction by impairing alveolar gas exchange; severe systemic inflammation contributes to sepsis and end-organ dysfunction (6). Pneumonia is the most common cause of ARDS (2, 7), an often fatal complication characterized by a dysregulated immune response (8, 9).

Systemic adjunctive corticosteroid therapy may attenuate the inflammatory response (10, 11) and, by doing so, reduce the frequency of ARDS, length of illness and hospital stay, and possibly even mortality. However, previous systematic reviews of randomized clinical trials have failed to establish a conclusive benefit (12, 13), and current clinical practice guidelines do not recommend systemic corticosteroid therapy for CAP (14, 15).

In light of recently published randomized trials (16, 17), we performed a systematic review and meta-analysis evaluating the effect of adjunctive corticosteroid therapy for patients hospitalized with CAP.

METHODS

Data Sources and Searches

A previous Cochrane review with similar inclusion criteria identified studies up to December 2010 (13). Using the Medical Subject Headings terms "pneumonia" and "corticosteroid", we replicated the search strategy of that review (13) for MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (13)

See also:

Editorial comment 560

Web-Only
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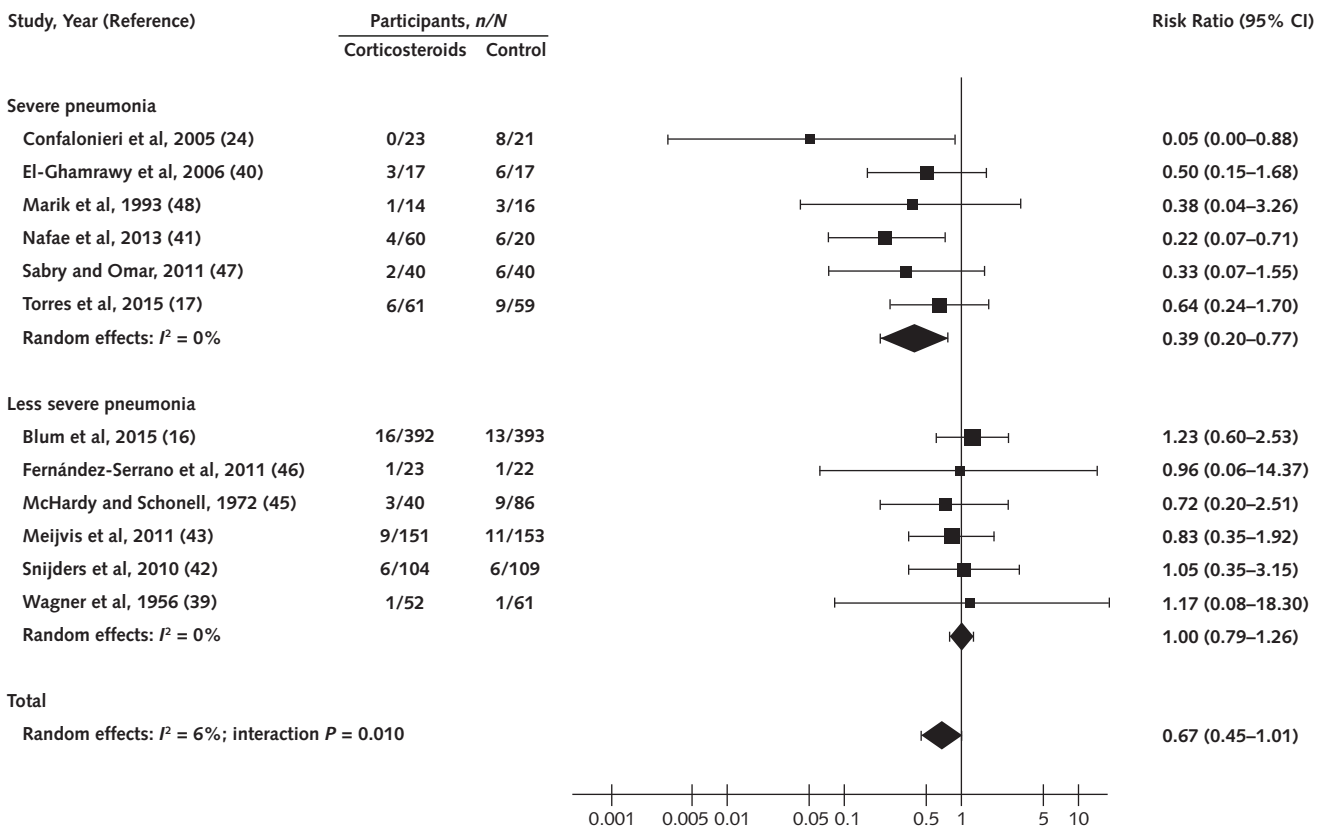
Figure 1. Effect of corticosteroids on all-cause mortality in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.



from 1 January 2010 to 24 May 2015. We manually searched the reference lists of included studies and existing systematic reviews as well as all articles citing the included studies on Google Scholar.

Study Selection

Eligible studies, reported in any language, randomly assigned adults with CAP to oral or intravenous corticosteroid therapy versus placebo or no treatment. We excluded studies of ventilator-associated pneumonia, aspiration pneumonia, or *Pneumocystis jirovecii* pneumonia and studies limited to patients with chronic obstructive pulmonary disease. Eligible studies reported on at least 1 of the following outcomes: duration of hospitalization, time to clinical stability, all-cause mortality, need for mechanical ventilation, need for intensive care unit (ICU) admission, or development of ARDS. Two teams of 2 reviewers independently screened titles and abstracts in duplicate, obtained full texts of articles that either reviewer considered potentially eligible, and determined eligibility from the full texts.

Data Abstraction and Quality Assessment

Two reviewers independently extracted data and assessed risk of bias. For all phases of the project, reviewers resolved disagreements by discussion and, as necessary, in consultation with a third reviewer.

In addition to measures of potential benefit, reviewers extracted data on possible harms, including rehospitalization, hyperglycemia requiring treatment, gastrointestinal hemorrhage, and severe neuropsychiatric symptoms (including delirium, psychosis, and mania). For studies reporting outcomes at more than 1 time point, we abstracted data closest to 30 days from randomization.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the certainty of evidence (also known as quality of evidence or confidence in evidence) for each outcome and for the entire body of evidence (18). Certainty of evidence takes into consideration the study design (in this case, randomized clinical trials); risk of bias, precision, consistency, and directness of the evidence; and the possibility of publication bias. A modified Cochrane instrument (19) provided the structure for assessing the risk of bias of the primary studies. We applied recently published methods to assess the effect of loss to follow-up (20, 21). Publication bias was assessed through visual inspection of funnel plots.

We used optimal information size calculations as an objective measure of imprecision for grading evidence, with an α of 0.05 and a β of 0.80 (22).

Data Synthesis and Analysis

We used random-effects models for all analyses (Mantel–Haenszel risk ratios [RRs] for dichotomous outcomes and mean differences for continuous variables). We hypothesized that the following would be associated with a larger treatment benefit: publication before 2000, greater pneumonia severity, longer duration of corticosteroid therapy (>3 vs. ≤3 days), and higher risk of bias. Conversion of nonparametric data to means and SDs was based on recently established methods (23). We conducted sensitivity analyses omitting studies in which means were estimated from medians and omitting 1 study that was stopped early for a large effect (24).

We defined severe pneumonia according to commonly used criteria (if available) in the following order of preference: Pneumonia Severity Index score of IV or V (25), CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, and age 65 years or older) score of 2 or greater (26), fulfillment of 1 major or 3 minor criteria from the 2007 consensus guideline from the Infectious Diseases Society of America and the American Thoracic Society (ATS) (14), a score of 3 or greater using British Thoracic Society criteria (27), fulfillment of 1 major or 2 minor criteria from the ATS 2001 rule (28), and meeting 1 of the ATS 1993 criteria (29). We used authors' classification of severe pneumonia when objective scoring was not available, and we classified individual studies as meeting the criteria for severe illness if at least 70% of patients had severe pneumonia at baseline (when data were available) or if mortality was at least 15% in the control group (when severity at presentation was not reported) (25).

Analyses were performed in Review Manager 5.2.7 (Cochrane Collaboration). Heterogeneity was assessed using visual inspection of the results, a test for heterogeneity, and the I^2 statistic (30). We calculated 95% CIs with the Hartung–Knapp–Sidik–Jonkman method, which is based on a *t* distribution (31, 32).

To estimate the absolute effects of the intervention on relevant outcomes, we sought large observational studies providing best estimates of these outcomes in the absence of corticosteroid therapy in representative patients with CAP (33). Reliable observational data were available for mortality (34), need for mechanical ventilation (35), admission to an ICU (35), ARDS (36), and rehospitalization (37). When observational data were not available, we used the median absolute effect from the control groups of trials (33, 38). As per GRADE guidelines, we then applied point estimates of relative effects and the associated CIs to estimate the absolute effects of the intervention.

Role of the Funding Source

This study received no external funding.

RESULTS

The literature search identified 3281 unique citations plus 3 studies identified from references 39 through 41 and 6 studies included in the previous review (2 of which were ineligible) (13) (**Appendix Figure 1**, available at www.annals.org). We included a total of 13 randomized, controlled trials (2005 patients), with 9 studies not included in the previous review (**Appendix Table 1**, available at www.annals.org).

Study Characteristics

Primary studies were conducted mostly in Europe, and only 1 received funding from the pharmaceutical industry (42). Sample sizes ranged from 30 to 784 hos-

Figure 2. Effect of corticosteroids on need for mechanical ventilation in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.

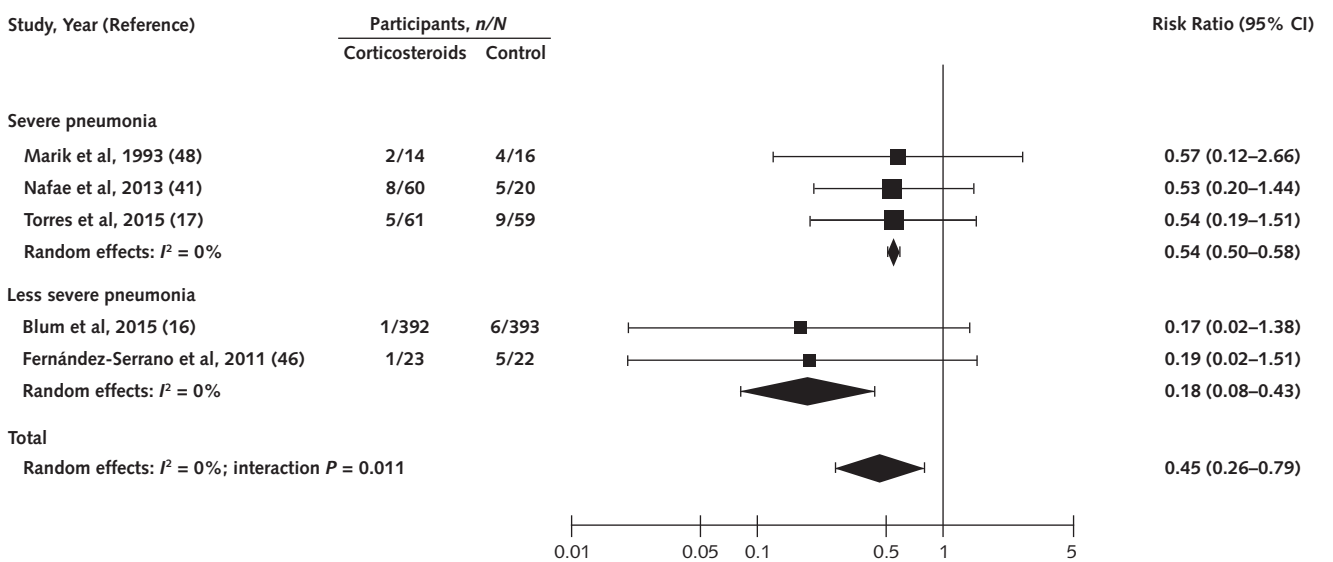
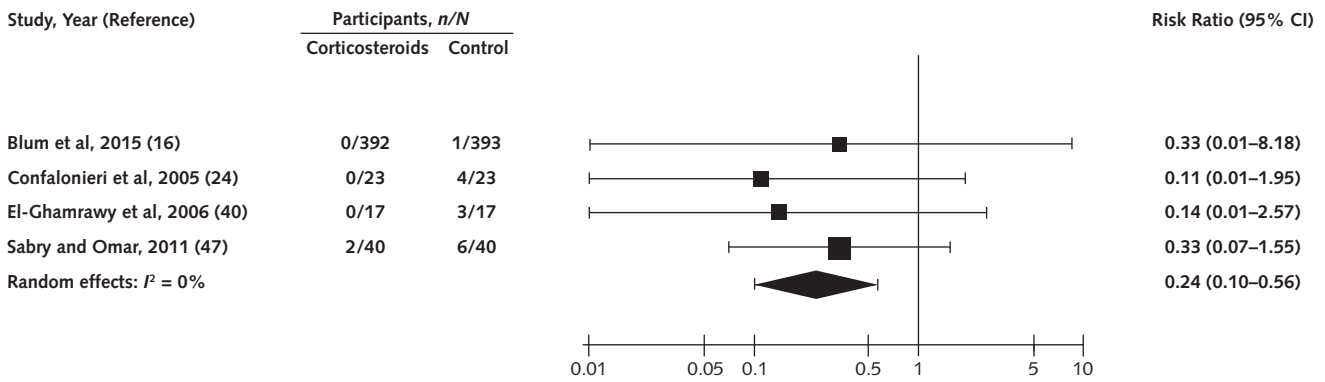


Figure 3. Effect of corticosteroids on development of the acute respiratory distress syndrome in patients hospitalized with community-acquired pneumonia.



pitalized patients, most of whom were men at a median age typically in the early 60s (Appendix Table 1) (34–37). Patients received corticosteroid treatment—dexamethasone (43), prednisone (16), prednisolone (42, 44, 45), methylprednisolone (17, 46), or hydrocortisone (24, 39–41, 47, 48)—ranging from 1 dose (48) to 10 days (24). A placebo was used in the control group in all studies. Follow-up ranged from in-hospital to 60 days from enrollment (Appendix Table 1). Studies often excluded patients at high risk for adverse effects from corticosteroids, including those with gastrointestinal hemorrhage within 3 months (16, 17, 24, 40, 41, 45, 47), those with immunosuppression (16, 17, 24, 40–44, 46–48), and pregnant women (16, 40–43, 47) (Appendix Table 1).

Risk-of-Bias Assessment

Five of 13 trials enrolling 70.4% of the total sample had low risk of bias (Appendix Table 2, available at www.annals.org). Loss to follow-up was rare: 10 trials had complete follow-up, and only 1 had attrition greater than 5% (39) (Appendix Tables 3 to 5, available at www.annals.org). Worst plausible assumptions about the outcomes of patients lost to follow-up did not materially change the results.

We were not able to detect publication bias for any analysis; however, only 1 outcome (all-cause mortality) was addressed in 10 or more studies and was thus evaluable using funnel plots (Appendix Figure 2, available at www.annals.org).

Outcomes

All-Cause Mortality

In 12 trials that addressed all-cause mortality, 79 of 997 (7.9%) patients died in the control groups compared with 52 of 977 (5.3%) in the corticosteroid groups (RR, 0.67 [95% CI, 0.45 to 1.01]; I^2 = 6%; moderate certainty) (Figure 1 and Appendix Figure 3, available at www.annals.org). The subgroup analyses suggested that the effect varied according to severity of CAP. An apparent mortality benefit was observed in trials that met our criteria for severe pneumonia (6 studies; 388 patients; RR, 0.39 [CI, 0.20 to 0.77]; I^2 = 0%) but not in those that did not (6 studies; 1586 patients; RR, 1.00 [CI, 0.79 to 1.26]; I^2 = 0%) (P = 0.010 for interaction) (Appendix Table 6, available at www.annals.org). Certainty of evidence was rated moderate because the CI crossed 1 and because of a possible subgroup effect.

Mechanical Ventilation

Five studies (1060 patients) found a reduction in the need for mechanical ventilation in patients who received corticosteroids (RR, 0.45 [CI, 0.26 to 0.79]; I^2 = 0%; moderate certainty) (Figure 2 and Appendix Figure 4, available at www.annals.org). Certainty of evidence was rated down because of a small number of events (46 total). The relative reduction in the need for mechanical ventilation was larger in studies enrolling patients with less severe pneumonia (RR, 0.18 [CI, 0.08 to 0.43]) than in those enrolling patients with severe pneumonia (RR, 0.54 [CI, 0.50 to 0.58]) (P = 0.011 for interaction) (Appendix Table 7, available at www.annals.org).

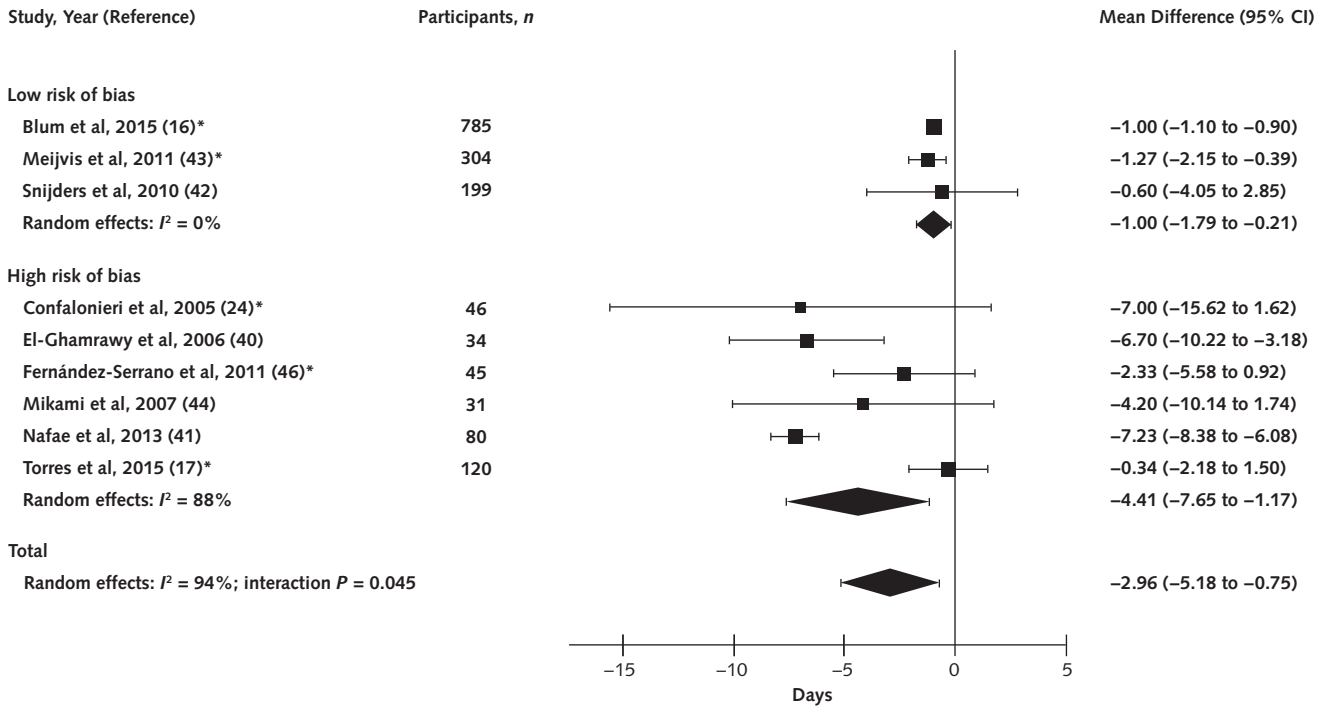
ICU Admission

Three studies (950 patients), all published after 2000, provided data on admission to an ICU among patients who were not in an ICU at enrollment. In all 3 studies, most patients had less severe CAP, and corticosteroid therapy was administered for more than 3 days. The results were consistent with the reduction in mechanical ventilation but with wider CIs (RR, 0.69 [CI, 0.46 to 1.03]; I^2 = 0; moderate certainty) (Appendix Figure 5 and Appendix Table 8, available at www.annals.org).

ARDS

Four studies (945 patients) evaluated risk for ARDS in patients who did not meet criteria at enrollment. Three (24, 41, 47) defined ARDS by consensus criteria

Figure 4. Effect of corticosteroids on duration of hospitalization in patients with community-acquired pneumonia, by study risk of bias.



* Mean length of stay is estimated from the median.

(49); the fourth did not specify diagnostic criteria (16). Results showed a statistically significant reduction in the risk for ARDS with corticosteroids (RR, 0.24 [CI, 0.10 to 0.56]; I^2 = 0%; moderate certainty) (Figure 3 and Appendix Table 9, available at www.annals.org). Certainty of evidence was rated down because of a small number of events (16 total).

Duration of Hospitalization

In all studies, patients were discharged at the discretion of the admitting physician. We estimated means from medians for 5 studies (16, 17, 24, 43, 46). We found a high degree of heterogeneity (I^2 = 94%) in the primary analysis of duration of hospitalization (Figure 4). Six trials (356 patients) were judged to be at high risk of bias, which explained the heterogeneity (P = 0.045 for interaction). Three studies (1288 patients) judged to be at low risk of bias showed a significant reduction in the length of hospitalization (mean difference, −1.00 day [CI, −1.79 to −0.21 days]; I^2 = 0%; high certainty) (Appendix Table 10, available at www.annals.org). We found no evidence that changing as-

Figure 5. Effect of corticosteroids on hyperglycemia in patients hospitalized with community-acquired pneumonia.

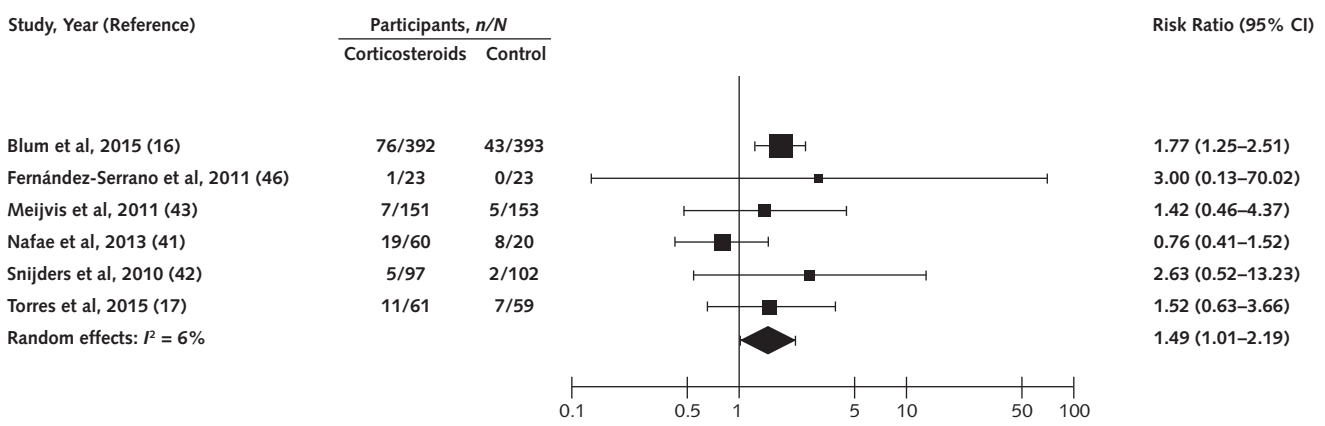


Table. GRADE Evidence Profile: Corticosteroids for Patients Hospitalized With Community-Acquired Pneumonia*

Outcome	Quality Assessment						
	Participants (Studies), *n*	Median Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias
All-cause mortality	1974 (12)	In-hospital	No serious limitations	Possible important subgroup differences‡	No serious limitations	Serious imprecision‡	Undetected
Need for mechanical ventilation	1060 (5)	In-hospital	No serious limitations	No serious limitations	No serious limitations	Serious limitations; small number of events	Undetected
Admission to ICU	950 (3)	30 d	No serious limitations	No serious limitations	No serious limitations	Serious imprecision; may be important undetected effect	Undetected
ARDS	945 (4)	30 d	No serious limitations	No serious limitations	No serious limitations	Serious limitations; small number of events	Undetected
Duration of hospitalization	1288 (3)	–	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected
Time to clinical stability	1180 (5)	–	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected
Hyperglycemia requiring treatment	1534 (6)	30 d	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected
Gastrointestinal hemorrhage	1223 (7)	In-hospital	No serious limitations	No serious limitations	No serious limitations	Serious imprecision; may be important undetected effect	Undetected
Severe neuropsychiatric complications¶	1217 (4)	30 d	No serious limitations	No serious limitations	Serious indirectness; lack of consistent and objective diagnostic criteria	Serious imprecision; may be important undetected effect	Undetected
Rehospitalization	1089 (2)	30 d	No serious limitations	No serious limitations	No serious limitations	Serious imprecision; may be important undetected effect	Undetected

ARDS = acute respiratory distress syndrome; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ICU = intensive care unit; RR = risk ratio.
* Adapted with permission from http://isof2.epistemonikos.org/#/finding/550bc6acf30d0c43083e63a0.
† Except where noted.
‡ We considered rating down this outcome for imprecision in addition to inconsistency because of a small number of events and because the number of included patients was smaller than the calculated optimal information size (n = 3500) to detect a relative reduction of 30%. However, given that other critical outcomes showed a benefit that would merit corticosteroid treatment insofar as there was no increase in mortality, we chose to rate down from "high" to "moderate."
§ Estimated from observational data (available in associated reference).
‖ Estimated from the median absolute effect of control groups of included studies. Absolute estimates may be underestimated because trials often excluded patients with risk factors for adverse events (e.g., recent gastrointestinal hemorrhage or uncontrolled diabetes).
¶ Includes psychosis, mania, and delirium.

sumptions, including using the median instead of the mean difference, had an important effect on outcomes (**Appendix Figure 6** and **Appendix Table 11**, available at www.annals.org). Two of 3 studies at low risk of bias (1089 patients) reported medians; each reported a statistically significant median reduction in hospitalization of 1 day with nonparametric testing (16, 43).

Time to Clinical Stability

Five studies (1180 patients) evaluated time to clinical stability, most often defined by the consensus criteria as having all vital signs within the normal range and not requiring supplemental oxygen (28). We estimated the mean from the median in 3 studies (16, 17, 46). The pooled results showed a significant reduction in the time to clinical stability (mean difference, −1.22 days [CI, −2.08 to −0.35 days]; I^2 = 38%; high certainty) (**Appendix Figure 7** and **Appendix Table 12**, available at www.annals.org). Sensitivity analyses of nonparametric data did not show a meaningful effect on the results (**Appendix Table 13** and **Appendix Figure 8**, available at www.annals.org).

Adverse Effects

Corticosteroid use increased the incidence of hyperglycemia requiring treatment (6 studies; 1534 patients; RR, 1.49 [CI, 1.01 to 2.19]; I^2 = 6%; high certainty) (**Figure 5** and **Appendix Table 14**, available at www.annals.org). Results did not show an effect of systemic corticosteroids on gastrointestinal hemorrhage (7 studies; 1223 patients) (**Appendix Figure 9** and **Appendix Table 15**, available at www.annals.org), severe neuropsychiatric complications (4 studies; 1217 patients) (**Appendix Figure 10** and **Appendix Table 16**, available at www.annals.org), or rehospitalization (2 studies; 1089 patients) (**Appendix Figure 11**, available at www.annals.org), although CIs around relative effects were wide. Most studies excluded patients at higher risk for adverse effects from corticosteroids (**Appendix Table 1**).

Subgroup Analysis

Risk of bias, year of publication, severity of pneumonia at enrollment, and duration of corticosteroid

Table–Continued

Summary of Findings					Certainty of Evidence
Study Event Rates, *n/N (%)*		RR (95% CI)†	Estimation of Absolute Effects		
Control	Corticosteroids		Control	Corticosteroids	
79/997 (7.9)	52/977 (5.3)	0.67 (0.45 to 1.01)	8.5% (34)§	2.8% fewer (4.8% fewer to 0.1% more)	Moderate
29/510 (5.7)	17/550 (3.1)	0.45 (0.26 to 0.79)	9.1% (35)§	5.0% fewer (6.7% to 1.9% fewer)	Moderate
36/474 (7.6)	25/476 (5.3)	0.69 (0.46 to 1.03)	13.4% (35)§	Not significant; 4.2% fewer (7.2% fewer to 0.4% more)	Moderate
14/472 (3.0)	2/473 (0.4)	0.24 (0.10 to 0.56)	8.1% (36)§	6.2% fewer (7.3% to 3.6% fewer)	Moderate
9.1 d	7.9 d	Mean difference, −1.00 d (−1.79 to −0.21 d)	9.1 d	1.0 fewer day (1.8 to 0.2 fewer days)	High
4.7 d	3.5 d	Mean difference, −1.22 d (−2.08 to −0.35 d)	4.7 d	1.2 fewer days (2.1 to 0.4 fewer days)	High
50/640 (7.7)	88/640 (13.8)	1.49 (1.01 to 2.19)	7.1%‖	3.5% more (0.1% to 8.5% more)	High
9/595 (1.5)	8/628 (1.3)	0.82 (0.33 to 1.62)	1.7%‖	Not significant; 0.3% fewer (1.1% fewer to 1.1% more)	Moderate
8/615 (1.3)	13/602 (2.2)	1.65 (0.88 to 3.08)	1.7%‖	Not significant; 1.1% more (0.2% fewer to 3.5% more)	Low
35/546 (6.4)	39/543 (7.2)	1.12 (0.59 to 2.13)	7.3% (37)§	Not significant; 0.9% more (3.0% fewer to 8.2% more)	Moderate

therapy did not show a consistent interaction across outcomes.

Sensitivity Analysis

One study was stopped early for benefit after 7 in-hospital deaths in the placebo group versus 0 deaths in the corticosteroid group (24). Omission of this study had no appreciable effect on the results. Omission of studies in which means were estimated from median values for continuous outcomes had a negligible effect on the results. Optimal information size was below the threshold for precision for all outcomes except duration of hospitalization and time to clinical stability (**Appendix Table 17**, available at www.annals.org).

DISCUSSION

Our findings show moderate certainty of an absolute reduction of approximately 5% in the need for mechanical ventilation and the rate of ARDS (and a corresponding number needed to treat of approximately 20) with systemic corticosteroid therapy in adult patients hospitalized for CAP (**Figures 2** and **3** and **Table**). This review also shows with high certainty that systemic corticosteroid therapy reduces time to clinical stability and duration of hospitalization by approximately 1 day (**Figure 4**, **Appendix Figure 7**, and **Table**). Our estimate for duration of hospitalization comes from studies at low risk of bias; the estimate of effect from all studies is larger (**Figure 4**). We found that adjunctive corticosteroids increase the incidence of hyperglycemia requiring treatment by approximately 4% (high certainty). A plain-language interactive summary of the findings table is available at http://isof2.epistemonikos.org/#/finding/550bc6acf30d0c43083e63a0.

Our meta-analysis showed a possible reduction in mortality with the use of corticosteroids (**Figure 1** and **Table**), but the certainty of this effect for all patients is diminished by the fact that it seemed to be driven by the subgroup of trials examining severe pneumonia (moderate certainty) (**Figure 1** and **Appendix Table 6**). However, the finding of the subgroup gains credibility from the large magnitude of effect, its biological plausibility (a greater inflammatory response in more severe pneumonia), and a small interaction *P* value (0.010). However, it is based on differences between rather than within studies; is driven, to a considerable extent, by a small study that was stopped early for benefit (24); and almost certainly represents a large overestimate of effect (50, 51). Furthermore, we found no consistency in the subgroup effect with related outcomes; studies enrolling patients with more severe illness did not show larger effects on the need for mechanical ventilation or risk for ARDS than those enrolling patients with less severe illness. In summary, although the subgroup effect may be real and there may be a mortality benefit with adjunctive corticosteroids restricted to those with severe pneumonia, established criteria for evaluating subgroup analyses suggest that the apparent effect is probably spurious (52, 53).

We also identified a possible subgroup effect on mechanical ventilation—studies of less severe pneumonia showed a larger relative reduction in the need for mechanical ventilation (relative risk reduction, 82% vs. 46%; $P = 0.011$ for interaction). However, this finding is probably spurious for the same reasons as those stated for the subgroup effect for mortality. Indeed, that the subgroup effects were opposite (that is, greater reduction in mortality among patients with severe pneumonia vs. greater reduction in mechanical ventilation among those with less severe illness) further reduces the credibility of both subgroup inferences.

Our study has several strengths. We developed explicit eligibility criteria, conducted a comprehensive search, assessed eligibility and risk of bias in duplicate, addressed all important outcomes, conducted a small number of plausible subgroup and sensitivity analyses, and applied GRADE criteria to determine certainty of evidence. In addition, we performed a "rapid meta-analysis," which included studies from a previous systematic review (13) and systematically searched literature published after the previous review. Although this method is new and not yet validated, it avoids unnecessary replication of previous work. However, our search was rigorous enough to find 2 trials (39, 40) that were missed in the previous review (13).

Our review also has limitations, including the use of various agents, routes of administration, and doses of corticosteroids in the included studies, leaving the optimal choice of agent and dose open to question. Moreover, we did not search the gray literature or conference abstracts, which may have provided additional studies; however, we believe that this is a minor issue.

Most primary studies excluded patients who were immunosuppressed, were pregnant, had recent gastrointestinal hemorrhage, or may have been at high risk for neuropsychiatric adverse effects. Application of our findings to these populations is therefore questionable. Inferences are also limited for outcomes with a small number of events (need for mechanical ventilation, admission to an ICU, and particularly ARDS). Finally, we could not rule out publication bias.

We used mean differences for continuous outcomes, although reductions in length of stay or time to clinical stability are unlikely to be normally distributed. However, our findings were robust to various sensitivity analyses.

We used the same methods as in our primary search (to 24 May 2015) to identify previous systematic reviews and meta-analyses. Our results are consistent with those of prior systematic reviews of corticosteroids in CAP (12, 13, 54), although inclusion of recent trials allowed us to address additional outcomes, including the need for mechanical ventilation, and to provide evidence resulting in greater certainty. Our finding of a reduction in hospital stay of approximately 1 day is similar to the effect of corticosteroids on duration of stay in patients having exacerbations of chronic obstructive pulmonary disease (55). A previous systematic review of randomized trials did not show an effect of corticosteroids on prevention of ARDS (56). However, these early trials had broad inclusion criteria, including patients with trauma, malignant tumor, hemorrhage, and nonpulmonary sepsis in addition to those with pneumonia (56, 57).

Our results provide high-quality evidence for the benefits of adjunctive corticosteroids in CAP. For many key outcomes, trials with low risk of bias provided much of the evidence; results are consistent across studies and are directly applicable to a broad range of patients with CAP (**Table**). The similar effects across related corticosteroid administration strategies and outcomes (length of hospital stay and achievement of clinical stability, need for mechanical ventilation, development of ARDS, need for ICU admission, and mortality) strengthen the credibility of the findings. The moderate certainty about some important outcomes does not decrease our high certainty of the benefits overall because, regardless of a possible absence of benefit on those outcomes (such as mortality), the benefits of steroids still outweigh the harms. We therefore rated the overall certainty of the available evidence as high for the benefits of adjunctive corticosteroids in CAP.

A recent trial restricted participation to patients with evidence of ongoing inflammation (17), an approach advocated by some experts; however, this was the sole trial with this restriction in our review. We did not consider microbiologic etiology in our review because it is not typically known when the decision to administer corticosteroids is made. Therefore, effects may vary by the underlying cause; however, our review applies to empirical therapy in all patients hospitalized with CAP.

The apparent benefits of systemic corticosteroids in CAP are large enough—a decrease in hospital stay of approximately 1 day and an absolute reduction in risk for mechanical ventilation of 5%—to be considered important by many. Given the frequency of CAP, and thus the associated economic burden (3, 4), routine use of corticosteroids for CAP could result in considerable cost savings. Although the need for treatment of hyperglycemia increased by 6%, we found no identifiable long-term adverse consequences. One trial documented no significantly increased risk for diabetes or use of glycemic agents 30 days after presentation (16).

The case for corticosteroids is stronger with more severe pneumonia. This result stems less from the suggestion of a subgroup effect on mortality (an effect with modest credibility) than from the higher incidence of ARDS and the need for mechanical ventilation and because mortality equates to a greater absolute risk reduction with corticosteroid use.

High-quality evidence shows an appreciable decrease in the duration of hospitalization with corticosteroid therapy, and moderate-quality evidence supports a substantial reduction in the need for mechanical ventilation, progression to ARDS, and mortality. Larger pragmatic trials could improve certainty associated with several important outcomes, including mortality, need for mechanical ventilation, ARDS, gastrointestinal bleeding, and neuropsychiatric disturbance. Decision

makers should seriously consider the use of corticosteroids in patients hospitalized with CAP, particularly in those who are more severely affected.

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References

1. **GBD 2013 Mortality and Causes of Death Collaborators.** Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385:117-71. [PMID: 25530442] doi:10.1016/S0140-6736(14)61682-2

2. **Estenssoro E, Dubin A, Laffaire E, Canales H, Sáenz G, Moseinco M, et al.** Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. Crit Care Med. 2002;30:2450-6. [PMID: 12441753]

3. **Thomas CP, Ryan M, Chapman JD, Stason WB, Tompkins CP, Suaya JA, et al.** Incidence and cost of pneumonia in Medicare beneficiaries. Chest. 2012;142:973-81. [PMID: 22406959]

4. **Welte T, Torres A, Nathwani D.** Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67:71-9. [PMID: 20729232] doi:10.1136/thx.2009.129502

5. **van der Poll T, Opal SM.** Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet. 2009;374:1543-56. [PMID: 19880020] doi:10.1016/S0140-6736(09)61114-4

6. **Rittirsch D, Flierl MA, Ward PA.** Harmful molecular mechanisms in sepsis. Nat Rev Immunol. 2008;8:776-87. [PMID: 18802444] doi:10.1038/nri2402

7. **Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al; OSCILLATE Trial Investigators.** High-frequency oscillation in early acute respiratory distress syndrome. N Engl J Med. 2013;368:795-805. [PMID: 23339639] doi:10.1056/NEJMoa1215554

8. **Erickson SE, Martin GS, Davis JL, Matthay MA, Eisner MD; NIH NHLBI ARDS Network.** Recent trends in acute lung injury mortality: 1996–2005. Crit Care Med. 2009;37:1574-9. [PMID: 19325464] doi:10.1097/CCM.0b013e31819fefdf

9. **Piantadosi CA, Schwartz DA.** The acute respiratory distress syndrome. Ann Intern Med. 2004;141:460-70. [PMID: 15381520] doi:10.7326/0003-4819-141-6-200409210-00012

10. **Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, et al.** Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Eur Respir J. 1999;14:218-20. [PMID: 10489855]

11. **Remmelts HH, Meijvis SC, Biesma DH, van Velzen-Blad H, Voorn GP, Grutters JC, et al.** Dexamethasone downregulates the systemic cytokine response in patients with community-acquired pneumonia. Clin Vaccine Immunol. 2012;19:1532-8. [PMID: 22855392] doi:10.1128/CVI.00423-12

12. **Nie W, Zhang Y, Cheng J, Xiu Q.** Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. PLoS One. 2012;7:e47926. [PMID: 23112872] doi:10.1371/journal.pone.0047926

13. **Chen Y, Li K, Pu H, Wu T.** Corticosteroids for pneumonia. Cochrane Database Syst Rev. 2011:CD007720. [PMID: 21412908] doi:10.1002/14651858.CD007720.pub2

14. **Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al; Infectious Diseases Society of America.** Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2:S27-72. [PMID: 17278083]

15. **Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases.** Guidelines for the management of adult lower respiratory tract infections–full version. Clin Microbiol Infect. 2011;17 Suppl 6:E1-59. [PMID: 21951385] doi:10.1111/j.1469-0691.2011.03672.x

16. **Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, et al.** Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2015;385:1511-8. [PMID: 25608756] doi:10.1016/S0140-6736(14)62447-8

17. **Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al.** Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015;313:677-86. [PMID: 25688779] doi:10.1001/jama.2015.88

18. **Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al; GRADE Working Group.** GRADE: an emerging consensus on rating quality of evidence and strength of recommendations.BMJ.2008;336:924-6.[PMID:18436948]doi:10.1136/bmj.39489.470347.AD

19. **Busse JW, Guyatt G.** Modification of Cochrane tool to assess risk of bias in randomized trials. 2013. Accessed at https://distillercer.com/wp-content/uploads/2014/02/Tool-to-Assess-Risk-of-Bias-in-Randomized-Controlled-Trials.docx on 24 June 2015.

20. **Akl EA, Johnston BC, Alonso-Coello P, Neumann I, Ebrahim S, Briel M, et al.** Addressing dichotomous data for participants excluded from trial analysis: a guide for systematic reviewers. PLoS One. 2013;8:e57132. [PMID: 23451162] doi:10.1371/journal.pone.0057132

21. **Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, et al.** Addressing continuous data measured with different instruments for participants excluded from trial analysis: a guide for systematic reviewers. J Clin Epidemiol. 2014;67:560-70. [PMID: 24613497] doi:10.1016/j.jclinepi.2013.11.014

22. **Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al.** GRADE guidelines 6. Rating the quality of evidence–imprecision. J Clin Epidemiol. 2011;64:1283-93. [PMID: 21839614] doi:10.1016/j.jclinepi.2011.01.012

23. **Wan X, Wang W, Liu J, Tong T.** Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135. [PMID: 25524443] doi:10.1186/1471-2288-14-135

24. **Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al.** Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med. 2005;171:242-8. [PMID: 15557131]

25. **Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al.** A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med. 1997;336:243-50. [PMID: 8995086]

26. **Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al.** Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-82. [PMID: 12728155]

27. **British Thoracic Society Standards of Care Committee.** BTS guidelines for the management of community acquired pneumonia in adults. Thorax. 2001;56 Suppl 4:IV1-64. [PMID: 11713364]

28. **Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al; American Thoracic Society.** Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med. 2001;163:1730-54. [PMID: 11401897]
29. **Niederman MS, Bass JB Jr, Campbell GD, Fein AM, Grossman RF, Mandell LA, et al.** Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society. Medical Section of the American Lung Association. Am Rev Respir Dis. 1993;148:1418-26. [PMID: 8239186]
30. **Higgins JPT, Altman DG.** Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. Chichester, United Kingdom: J Wiley; 2009.
31. **IntHout J, Ioannidis JP, Borm GF.** The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. BMC Med Res Methodol. 2014;14:25. [PMID: 24548571] doi:10.1186/1471-2288-14-25
32. **Knapp G, Hartung J.** Combined test procedures in the meta-analysis of controlled clinical trials. Stud Health Technol Inform. 2000;77:34-8. [PMID: 11187570]
33. **Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, Furukawa TA, et al.** GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol. 2013;66:173-83. [PMID: 23116689] doi:10.1016/j.jclinepi.2012.08.001
34. **Yu H, Rubin J, Dunning S, Li S, Sato R.** Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. J Am Geriatr Soc. 2012;60:2137-43. [PMID: 23110409] doi:10.1111/j.1532-5415.2012.04208.x
35. **Charles PG, Wolfe R, Whitby M, Fine MJ, Fuller AJ, Stirling R, et al; Australian Community-Acquired Pneumonia Study Collaboration.** SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. Clin Infect Dis. 2008;47:375-84. [PMID: 18558884] doi:10.1086/589754
36. **Toba A, Yamazaki M, Mochizuki H, Noguchi T, Tsuda Y, Kawate E, et al.** Lower incidence of acute respiratory distress syndrome in community-acquired pneumonia patients aged 85 years or older. Respirology. 2010;15:319-25. [PMID: 20070586] doi:10.1111/j.1440-1843.2009.01685.x
37. **Capelastegui A, España Yandiola PP, Quintana JM, Bilbao A, Diez R, Pascual S, et al.** Predictors of short-term rehospitalization following discharge of patients hospitalized with community-acquired pneumonia. Chest. 2009;136:1079-85. [PMID: 19395580] doi:10.1378/chest.08-2950
38. **Tikkinen KA, Agarwal A, Craigie S, Cartwright R, Gould MK, Haukka J, et al.** Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. Syst Rev. 2014;3:150. [PMID: 25540016] doi:10.1186/2046-4053-3-150
39. **Wagner HN Jr, Bennett IL Jr, Lasagna L, Cluff LE, Rosenthal MB, Mirick GS.** The effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. Bull Johns Hopkins Hosp. 1956;98:197-215. [PMID: 13304518]
40. **El-Ghamrawy AH, Shokeir MH, Esmat AA.** Effects of low-dose hydrocortisone in ICU patients with severe community-acquired pneumonia. Egyptian Journal of Chest. 2006;55:91-9.
41. **Nafae RM, Ragab MI, Amany FM, Rashed SB.** Adjuvant role of corticosteroids in the treatment of community-acquired pneumonia. Egyptian Journal of Chest Diseases and Tuberculosis. 2013;62:439-45.
42. **Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG.** Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010;181:975-82. [PMID: 20133929] doi:10.1164/rccm.200905-0808OC
43. **Meijvis SC, Hardeman H, Remmelts HH, Heijligenberg R, Rijkers GT, van Velzen-Blad H, et al.** Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377:2023-30. [PMID: 21636122] doi:10.1016/S0140-6736(11)60607-7
44. **Mikami K, Suzuki M, Kitagawa H, Kawakami M, Hirota N, Yamaguchi H, et al.** Efficacy of corticosteroids in the treatment of community-acquired pneumonia requiring hospitalization. Lung. 2007;185:249-55. [PMID: 17710485]
45. **McHardy VU, Schonell ME.** Ampicillin dosage and use of prednisolone in treatment of pneumonia: co-operative controlled trial. Br Med J. 1972;4:569-73. [PMID: 4404939]
46. **Fernández-Serrano S, Dorca J, Garcia-Vidal C, Fernández-Sabé N, Carratalà J, Fernández-Agüera A, et al.** Effect of corticosteroids on the clinical course of community-acquired pneumonia: a randomized controlled trial. Crit Care. 2011;15:R96. [PMID: 21406101] doi:10.1186/cc10103
47. **Sabry NA, Omar EE.** Corticosteroids and ICU course of community acquired pneumonia in Egyptian settings. Pharmacol Pharm. 2011;2:73-81.
48. **Marik P, Kraus P, Sribante J, Havlik I, Lipman J, Johnson DW.** Hydrocortisone and tumor necrosis factor in severe community-acquired pneumonia. A randomized controlled study. Chest. 1993;104:389-92. [PMID: 8339624]
49. **Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al.** The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149:818-24. [PMID: 7509706]
50. **Montori VM, Devereaux PJ, Adhikari NK, Burns KE, Eggert CH, Briel M, et al.** Randomized trials stopped early for benefit: a systematic review. JAMA. 2005;294:2203-9. [PMID: 16264162]
51. **Bassler D, Briel M, Montori VM, Lane M, Glasziou P, Zhou Q, et al; STOPIT-2 Study Group.** Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA. 2010;303:1180-7. [PMID: 20332404] doi:10.1001/jama.2010.310
52. **Oxman AD, Guyatt GH.** A consumer's guide to subgroup analyses. Ann Intern Med. 1992;116:78-84. [PMID: 1530753] doi:10.7326/0003-4819-116-1-78
53. **Sun X, Briel M, Walter SD, Guyatt GH.** Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117. [PMID: 20354011] doi:10.1136/bmj.c117
54. **Cheng M, Pan ZY, Yang J, Gao YD.** Corticosteroid therapy for severe community-acquired pneumonia: a meta-analysis. Respir Care. 2014;59:557-63. [PMID: 24046464] doi:10.4187/respcare.02758
55. **Walters JA, Tan DJ, White CJ, Gibson PG, Wood-Baker R, Walters EH.** Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;9:CD001288. [PMID: 25178099] doi:10.1002/14651858.CD001288.pub4
56. **Peter JV, John P, Graham PL, Moran JL, George IA, Bersten A.** Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. BMJ. 2008;336:1006-9. [PMID: 18434379] doi:10.1136/bmj.39537.939039.BE
57. **Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA.** Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest. 1987;92:1032-6. [PMID: 3315478]

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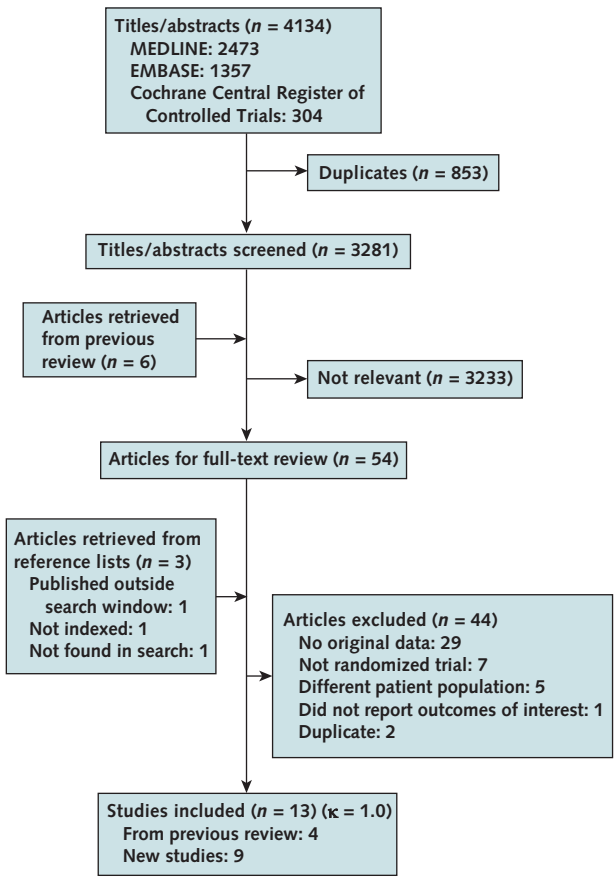
Appendix Figure 1. Summary of evidence search and selection.



Appendix Table 1. Study Characteristics

Study, Year (Reference)	Location	Patients, *n*	Mean Age (SD), *y*	Men, *n (%)*	Severity Score Used; Severe, *n (%)**	Patients With Known COPD, *n (%)*	Inclusion Criteria	Exclusion Criteria	Follow-up	Corticosteroid Agent, Dose, Route, and Duration
Blum, 2015 (16)	Switzerland	784	Median (IQR): 74 (61–83)	487 (62.0)	PSI; 386 (49.2)	133 (16.9)	Age ≥18 y, ATS criteria for CAP	Inability to consent IV drug use GI hemorrhage past 3 mo Adrenal insufficiency Any condition requiring moderate-dose corticosteroids Severe immunosuppression Acute burn Pregnancy	30 d	Prednisone 50 mg oral daily for 7 d
Confalonieri, 2005 (24)	Italy	46	63.5 (16.0)	32 (69.6)	ATS 1993; 46 (100)	3 (6.5)	CAP with 1993 ATS criteria severe	Severe immunosuppression Acute burn Life expectancy <3 mo Major GI hemorrhage past 3 mo Any condition requiring moderate-dose corticosteroids	60 d	Hydrocortisone 200 mg IV bolus followed by 10 mg/h IV for 10 d
El-Ghamrawy, 2006 (40)	Saudi Arabia	34	61.8 (14.7)	21 (61.8)	ATS 2001; 34 (100)	NR	Age ≥18 y, severe CAP by ATS criteria requiring ICU admission	Severe immunosuppression Acute burn Life expectancy <3 mo Major GI hemorrhage past 3 mo Any condition requiring moderate-dose corticosteroids Pregnancy	In-hospital	Hydrocortisone 200 mg IV bolus followed by 10 mg/h for 7 d
Fernández-Serrano, 2011 (46)	Spain	45	63.5 (range, 48–70)	30 (66.7)	PSI; 27 (60.0)	6 (13.3)	Age ≥18 and ≤75 y, severe CAP with consolidation of ≥2 lobes and Po_2/FIo_2 <300	Hypersensitivity to corticosteroids Any condition requiring corticosteroids Uncontrolled diabetes Active peptic ulcer Severe immunosuppression Presence of shock Empyema	1 mo	Methylprednisolone 200 mg IV bolus, followed by tapering infusion (3.3 to 0.8 mg/h IV) over 9 d
Marik, 1993 (48)	South Africa	30	36.2 (13.8)	NR	BTS; 30 (100)	NR	Age ≥18 and ≤70 y, BTS criteria for severe CAP	Receiving other immunosuppressive therapy Malignancy Active tuberculosis HIV	To discharge from ICU	Hydrocortisone 10 mg/kg IV 30 min before antibiotics
McHardy, 1972 (45)	Scotland	126	60.3	61 (48.4)	Clinical opinion; 20 (15.8)	21 (17.5)†	Age ≥12 y, clinical diagnosis of pneumonia	Severe disease, at risk for death within 24 h Diabetes Recent peptic ulceration	NR, likely in-hospital	Prednisolone 5 mg every 6 h orally for 7 d
Meijvis, 2011 (43)	The Netherlands	304	63.9 (18.5)	171 (56.4)	PSI; 143 (47.2)	34 (11.2)	Age ≥18 y, CAP by PSI criteria	Immunodeficiency Receiving chemotherapy Any corticosteroid within 6 wk Hematologic malignancy Pregnancy	30 d	Dexamethasone 5 mg IV daily for 4 d
Mikami, 2007 (44)	Japan	31	72.0 (19.5)	23 (74.2)	PSI; 17 (54.8)	0 (0)	Any CAP, nonsevere by ATS criteria	HIV Immunosuppression COPD Asthma treated with corticosteroids Dependent for ADLs Malignancy Cirrhosis Congestive heart failure	In-hospital	Prednisolone 40 mg IV daily for 3 d

Continued on following page

Appendix Table 1–Continued

Study, Year (Reference)	Location	Patients, *n*	Mean Age (SD), *y*	Men, *n (%)*	Severity Score Used; Severe, *n* (%)*	Patients With Known COPD, *n (%)*	Inclusion Criteria	Exclusion Criteria	Follow-up	Corticosteroid Agent, Dose, Route, and Duration
Nafae, 2013 (41)	Egypt	80	49.0 (13.3)	45 (56.3)	NR	NR	Age ≥18 y, PSI criteria for CAP	Immunosuppression HIV Acute burn Major GI hemorrhage within 3 mo Cirrhosis Requiring moderate doses of corticosteroids for another indication Pregnancy	In-hospital	Hydrocortisone 200 mg IV bolus followed by 10 mg/h IV for 7 d
Sabry, 2011 (47)	Egypt	80	62.2 (range, 50–72)	58 (72.3)	ATS 2007; 80 (100)	0 (0)	Adults with ATS criteria for severe CAP	Immunosuppression Congestive heart failure Chronic renal/hepatic disease Acute burn Major GI hemorrhage within 3 mo Pregnancy Concomitant infections	8 d	Hydrocortisone 200 mg IV bolus, then 12.5 mg/h IV for 7 d
Snijders, 2010 (42)	The Netherlands	213	63.5 (18.2)	124 (57.9)	PSI; 93 (44.7)	43 (20.2)	Age ≥18 y hospitalized with CAP	Severe immunosuppression HIV Malignancy Use of ≥15 mg of prednisone or equivalent Pregnancy Any indication patients could not comprehend protocol	30 d	Prednisolone 40 mg IV or orally for 7 d
Torres, 2015 (17)	Spain	120	65.3 (19.6)	74 (61.7)	PSI; 88 (73.3)	19 (15.8)	Age ≥18 y with severe CAP by ATS or PSI criteria and serum CRP level >150 mg/L	Prior systemic corticosteroid treatment Severe immunosuppression HIV Life expectancy <3 mo Uncontrolled diabetes mellitus Major GI hemorrhage within 3 mo Condition requiring >1 mg/kg per day methylprednisolone equivalent	In-hospital	Methylprednisolone 0.5 mg/kg IV twice daily for 5 d
Wagner, 1956 (39)	United States	113	52% <40 y	76 (67.3)	NR	NR	Culture-confirmed pneumococcal pneumonia	Meningitis Empyema	NR, likely in-hospital	Hydrocortisone 80–100 mg oral every 6 h tapering dose over 5 d

ADL = activities of daily living; ATS = American Thoracic Society; BTS = British Thoracic Society; CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CURB-65 = Confusion, Urea nitrogen, Respiratory rate, Blood pressure, and age 65 years or older; GI = gastrointestinal; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IQR = interquartile range; IV = intravenous; NR = not reported; PSI = Pneumonia Severity Index.

* Severe pneumonia is defined as PSI of IV or V, CURB-65 score ≥2; meeting 1 of the ATS 1993 criteria; ATS 2001 rule where 1 major or 2 minor criteria are satisfied; ATS-IDSA 2007 rule where 1 major or 3 minor criteria are satisfied; BTS score ≥3.

† "Severe chronic bronchitis."

Appendix Table 2. Quality Assessment: Low Versus High Risk of Bias*

Study, Year (Reference)	Allocation Adequately Concealed?	Adequate Blinding?†	Attrition Infrequent?‡	Free of Evidence of Selective Reporting?	Free of Other Significant Bias?	Industry-Funded	Overall Risk of Bias
Blum, 2015 (16)	Yes	Yes	Yes	Yes	Yes	No	Low
Confalonieri, 2005 (24)	Probably yes	Yes	Yes	Yes	No: trial stopped early	No	High
El-Ghamrawy, 2006 (40)	Probably no	Probably no	Yes	Yes	Yes	NR	High
Fernández-Serrano, 2011 (46)	Probably no	Probably yes	Yes	Probably yes	No: per protocol analysis	No	High
Marik, 1993 (48)	Probably yes	Probably yes	Yes	Yes	Yes	NR	Low
McHardy, 1972 (45)	Probably no	No	Probably no	Probably yes	No: per protocol analysis	No	High
Meijvis, 2011 (43)	Yes	Yes	Yes	Yes	Yes	No	Low
Mikami, 2007 (44)	Probably no	No	Yes	Probably yes	Probably yes	NR	High
Nafae, 2013 (41)	Probably yes	No	Yes	Yes	Yes	NR	High
Sabry, 2011 (47)	Probably yes	Yes	Yes	Yes	Yes	No	Low
Snijders, 2010 (42)	Yes	Yes	Yes	Probably yes	Yes	Yes	Low
Torres, 2015 (17)	Probably no	Yes	Yes	Yes	Yes	No	High
Wagner, 1956 (39)	No	Yes	Probably yes	Yes	No: per protocol selection	No	High

NR = not reported.
* Answers could be yes, probably yes, probably no, or no (19).
† Adequate blinding of patients and primary clinicians.
‡ Defined as <15% attrition to primary outcome and those excluded not likely to have made a material difference in outcomes.

Appendix Table 3. Mortality Data

Study, Year (Reference)	Included in Analysis (Intervention/Control), *n*	Follow-up	Mortality (Intervention/Control), *n (%)**	Pneumonia-Specific Mortality (Intervention/Control), *n (%)**
Blum, 2015 (16)	392/393	30 d	16 (4)/13 (3)	5 (1)/7 (2)
Confalonieri, 2005 (24)	23/21	60 d	0 (0)/8 (34.8)	0 (0)/8 (34.8)
El-Ghamrawy, 2006 (40)	17/17	In-hospital	3 (18)/6 (35)	NR
Fernández-Serrano, 2011 (46)	23/22	1 mo	1 (4.3)/1 (4.5)	NR
Marik, 1993 (48)	14/16	In-hospital	1 (7.1)/3 (18.8)	NR
McHardy, 1972 (45)	40/86	NR, likely in-hospital	3 (7.5)/9 (10.4)	2 (5.0)/4 (4.6)
Meijvis, 2011 (43)	151/153	30 d	9 (5.9)/11 (7.2)	6 (4.0)/6 (3.9)†
Mikami, 2007 (44)	15/16	In-hospital	NR	NR
Nafae, 2013 (41)	60/20	In-hospital	4 (6.7)/6 (31.6)	NR
Sabry, 2011 (47)	40/40	8 d	2 (5)/6 (15)	2 (5)/6 (15)
Snijders, 2010 (42)	104/109	30 d	6 (5.8)/6 (5.5)	NR
Torres, 2015 (17)	61/59	In-hospital	6 (10)/9 (15)	5 (8.2)/8 (13.6)
Wagner, 1956 (39)	52/61	In-hospital	1 (1.9)/1 (1.6)	NR

NR = not reported.
* Preference for 1 mo/30-d mortality, then any defined period closest to 30 d; however, abstract in-hospital mortality is reported if that was the only one available.
† Reviewer-abstracted data where cardiac arrest was thought to be pneumonia-specific and myocardial infarction was felt to be a non–pneumonia-specific cause of death. This is in-hospital mortality (higher risk of bias).

Appendix Table 4. Outcome Data

Study, Year (Reference)	Included in Analysis (Intervention/ Control), *n*	Follow-up	Required ICU Care (Intervention/ Control), *n (%)**	Required Mechanical Ventilation (Intervention/ Control), *n (%)**	Developed ARDS (Intervention/ Control), *n (%)*	Mean (SD) Duration of Mechanical Ventilation (Intervention/ Control), *d*	Mean (SD) Duration of Hospitalization (Intervention/ Control), *d*	Mean (SD) Time to Clinical Stability (Intervention/ Control), *d*†
Blum, 2015 (16)	392/393	30 d	16 (4.1)/22 (5.6)	1 (0.3)/6 (1.5)	0 (0)/1 (0.3)	–	6.3 (0.74)/7.3 (0.74)	3.0 (0.67)/4.5 (0.74)
Confalonieri, 2005 (24)	23/23	In-hospital	NA	NA	0 (0)/4 (17)	9.0 (7.5) (*n* = 15)/16.5 (11.3) (*n* = 19)	22.3 (11.2)/29.3 (17.9)	–
El-Ghamrawy, 2006 (40)	17/17	In-hospital	NA	NA	0 (0)/3 (18)	6.1 (1.4) (*n* = 11)/11.3 (2.9) (*n* = 10)	16.4 (3.9)/23.1 (6.3)	–
Fernández-Serrano, 2011 (46)	23/22	1 mo	4 (17.4)/5 (22.7)	1 (4.3)/5 (22.7)	–	3 (–) (*n* = 1)/15.3 (19.1) (*n* = 5)	10.67 (3.16)/13.00 (7.13)	4.3 (3.2)/6.7 (5.6)
Marik, 1993 (48)	14/16	In-hospital	NA	2 (14.3)/4 (25.0)	–	–	–	–
McHardy, 1972 (45)	40/86	NR, likely in-hospital	–	–	–	–	–	–
Meijvis, 2011 (43)	151/153	30 d	7 (4.6)/10 (6.5)	–	–	–	6.83 (2.99)/8.1 (4.64)	–
Mikami, 2007 (44)	15/16	In-hospital	–	–	–	–	11.3 (5.5)/15.5 (10.7)	4.2 (2.5)/6.3 (4.0)
Nafae, 2013 (41)	60/20	In-hospital	–	8 (13.3)/5 (25.0)	–	1.2 (3.75) (*n* = 8)/4.3 (7.83) (*n* = 5)	9.27 (2.4)/16.5 (2.24)	–
Sabry, 2011 (47)	40/40	8 d	NA	NA	2 (5)/6 (15)	4.6 (0.6) (*n* = 34)/6.8 (0.4) (*n* = 26)	NA	NA
Snijders, 2010 (42)	97/102	30 d	–	–	–	–	10.0 (12.0)/10.6 (12.8)	4.9 (6.8)/4.9 (5.2)
Torres, 2015 (17)	61/59	In-hospital (5 d for mechanical ventilation)	NA	5 (8.2)/9 (15.3)	–	–	10.8 (4.9)/11.2 (5.3)	4.3 (2.3)/5.0 (3.0)
Wagner, 1956 (39)	52/61	In-hospital	–	–	–	–	–	–

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; NA = not applicable; NR = not reported.

* Only included if the study enrolled all patients before ICU admission.

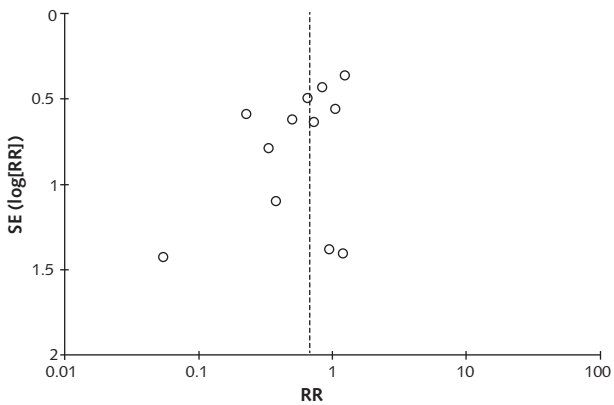
† Defined as having all vital signs stable for 24 h; if only reported separately, then time to peripheral capillary oxygen saturation ≥92% without supplemental oxygen, then time to resolution of morbidity (42).

Appendix Table 5. Safety Data

Study, Year (Reference)	Included in Analysis (Intervention/ Control), *n*	Follow-up	Rehospitalization After Discharge (Intervention/ Control), *n (%)*	Hyperglycemia Requiring Treatment (Intervention/ Control), *n (%)*	Gastrointestinal Bleeding (Intervention/ Control), *n (%)*	Severe Psychiatric Complications (Intervention/ Control), *n (%)**
Blum, 2015 (16)	392/393	30 d	32 (9)/28 (8)	76 (19.4)/43 (10.9)	3 (0.8)/4 (1.0)	5 (1.3)/2 (0.5)
Confalonieri, 2005 (24)	23/23	In-hospital	NR	NR	1 (4.3)/1 (4.3)	NR
El-Ghamrawy, 2006 (40)	17/17	In-hospital	NR	NR	2 (11.8)/1 (5.9)	NR
Fernández-Serrano, 2011 (46)	23/22	NR	NR	1 (4.3)/0 (0)	1 (4.3)/0 (0)	NR
Marik, 1993 (48)	14/16	NR	NR	NR	NR	NR
McHardy, 1972 (45)	40/86	NR	NR	NR	NR	NR
Meijvis, 2011 (43)	151/153	30 d	7 (5)/7 (5)	7 (4.6)/5 (3.3)	NR	NR
Mikami, 2007 (44)	15/16	In-hospital	NR	NR	NR	NR
Nafae, 2013 (41)	60/20	In-hospital	NR	19 (31.7)/8 (40.0)	1 (1.6)/1 (5.0)	NR
Sabry, 2011 (47)	40/40	8 d	NR	NR	NR	NR
Snijders, 2010 (42)	97/102	30 d	NR	5 (2.3)/2 (0.9)	NR	4 (1.9)/3 (1.4)
Torres, 2015 (17)	61/59	In-hospital	NR	11 (18.0)/7 (11.9)	0 (0)/1 (1.7)	1 (1.6)/0 (0)
Wagner, 1956 (39)	52/61	In-hospital	NR	NR	0 (0)/1 (1.6)	3 (5.8)/3 (4.9)

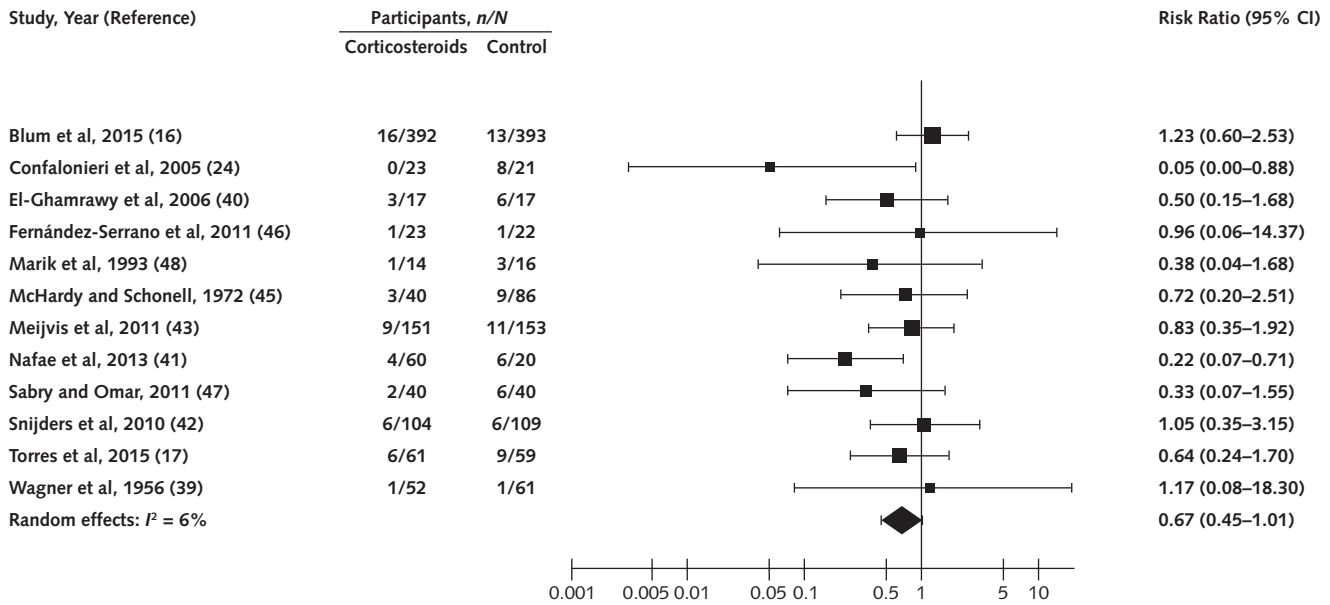
NR = not reported.
* Includes psychosis, mania, delirium, and severe mood changes.

Appendix Figure 2. All-cause mortality associated with corticosteroids in community-acquired pneumonia.



RR = risk ratio.

Appendix Figure 3. All-cause mortality associated with adjunctive corticosteroid therapy in patients with community-acquired pneumonia.

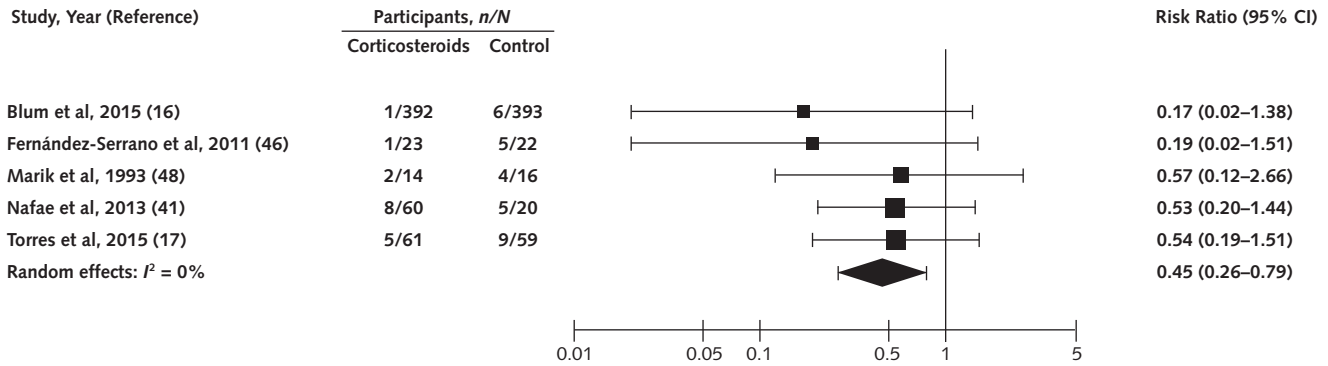


Appendix Table 6. Subgroup Analyses for Overall Mortality With Adjunctive Therapy for CAP

Subgroup, by Analysis	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	5	0.90 (0.50–1.62)	
High	7	0.47 (0.24–0.91)	0.152
Year			
≤2000	3	0.67 (0.23–1.93)	
≥2001	9	0.64 (0.37–1.09)	0.94
Severity			
Severe	6	0.39 (0.20–0.77)	
Not severe	6	1.00 (0.79–1.26)	0.010
Prescription duration			
≤3 d	1	0.38 (0.04–3.26)	
≥4 d	11	0.68 (0.44–1.06)	0.61
Confalonieri (24)			
Without	11	0.72 (0.50–1.04)	0.77
With	12		
Severe, Confalonieri (24)			
Without	5	0.51 (0.27–0.98)	
With	6	0.39 (0.20–0.77)	0.49

CAP = community-acquired pneumonia; RR = risk ratio.

Appendix Figure 4. Need for mechanical ventilation associated with adjunctive corticosteroid therapy in patients with community-acquired pneumonia.

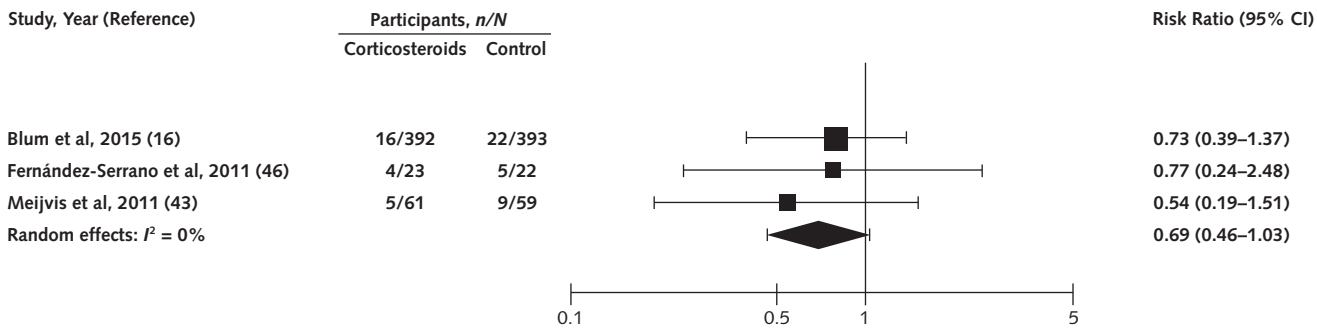


Appendix Table 7. Subgroup Analyses for Need for Mechanical Ventilation With Adjunctive Corticosteroid Therapy for CAP

Subgroup, by Analysis	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	2	0.37 (0.00–553.15)	
High	3	0.48 (0.18–1.27)	0.96
Year			
≤2000	1	0.57 (0.12–2.66)	
≥2001	4	0.43 (0.20–0.94)	0.75
Severity			
Severe	3	0.54 (0.50–0.58)	
Not severe	2	0.18 (0.08–0.43)	0.011
Prescription duration			
≤3 d	0	–	
≥4 d	5	–	–

CAP = community-acquired pneumonia; RR = risk ratio.

Appendix Figure 5. Need for intensive care unit admission associated with adjunctive corticosteroid therapy in patients with community-acquired pneumonia.



Appendix Table 8. Subgroup Analyses for Need for ICU Admission With Adjunctive Corticosteroid Therapy for CAP

Subgroup, by Analysis	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	2	0.67 (0.12–3.68)	
High	1	0.77 (0.24–2.48)	0.90
Year			
≤2000	0	–	
≥2001	3	–	–
Severity			
Severe	0	–	
Not severe	3	–	–
Prescription duration			
≤3 d	0	–	
≥4 d	3	–	–

CAP = community-acquired pneumonia; ICU = intensive care unit; RR = risk ratio.

Appendix Table 9. Subgroup Analyses for Development of ARDS With Adjunctive Corticosteroid Therapy for CAP

Subgroup, by Analysis	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	2	0.33 (0.29–0.38)	
High	2	0.13 (0.02–0.68)	0.30
Year			
≤2000	0	–	
≥2001	4	–	–
Severity			
Severe	3	0.23 (0.05–0.98)	
Not severe	1	0.33 (0.01–8.18)	0.85
Prescription duration			
≤3 d	0	–	
≥4 d	4	–	–
Confalonieri (24)			
Without	3	0.28 (0.10–0.77)	
With	4	0.24 (0.11–0.57)	0.82

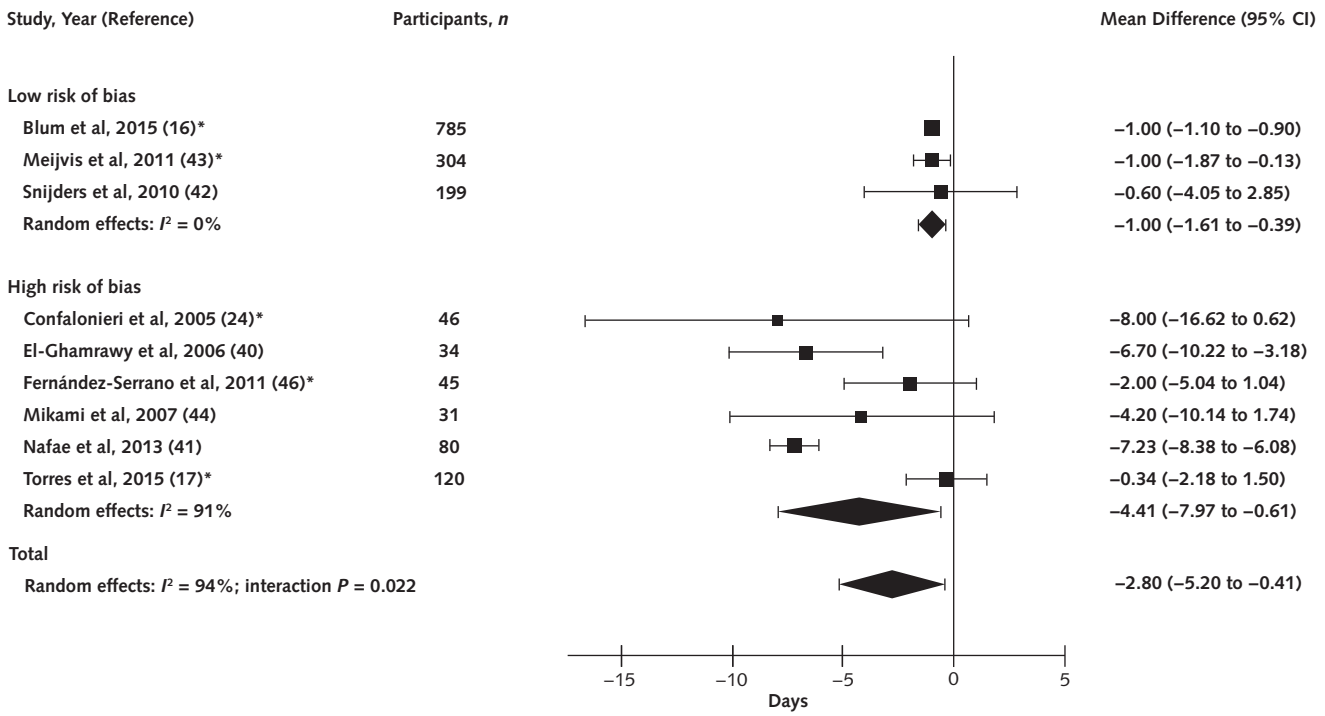
ARDS = acute respiratory distress syndrome; CAP = community-acquired pneumonia; RR = risk ratio.

Appendix Table 10. Subgroup Analyses for Mean Change in Duration of Hospitalization With Adjunctive Corticosteroid Therapy for CAP

Subgroup, by Analysis	Studies, *n*	Mean Difference (95% CI), *d*	*P* Value
Risk of bias			
Low	3	−1.00 (−1.79 to −0.21)	
High	6	−4.41 (−7.65 to −1.17)	0.045
Blinding			
Adequate	6	−1.00 (−2.74 to 0.74)	
Not adequate	3	−7.08 (−11.04 to −3.12)	0.006
Year			
≤2000	0	-	
≥2001	9	-	-
Severity			
Severe	4	−5.03 (−10.78 to 0.72)	
Not severe	5	−1.01 (−2.68 to 0.66)	0.188
Prescription duration			
≤3 d	1	−4.20 (−10.14 to 1.74)	
≥4 d	6	−2.88 (−5.37 to −0.39)	0.69
Estimated from medians			
Reported mean	4	−4.93 (−9.93 to 0.07)	
Reported median	5	−1.00 (−3.27 to 1.27)	0.161

CAP = community-acquired pneumonia.

Appendix Figure 6. Duration of hospitalization: sensitivity analysis with reported medians instead of imputed means.



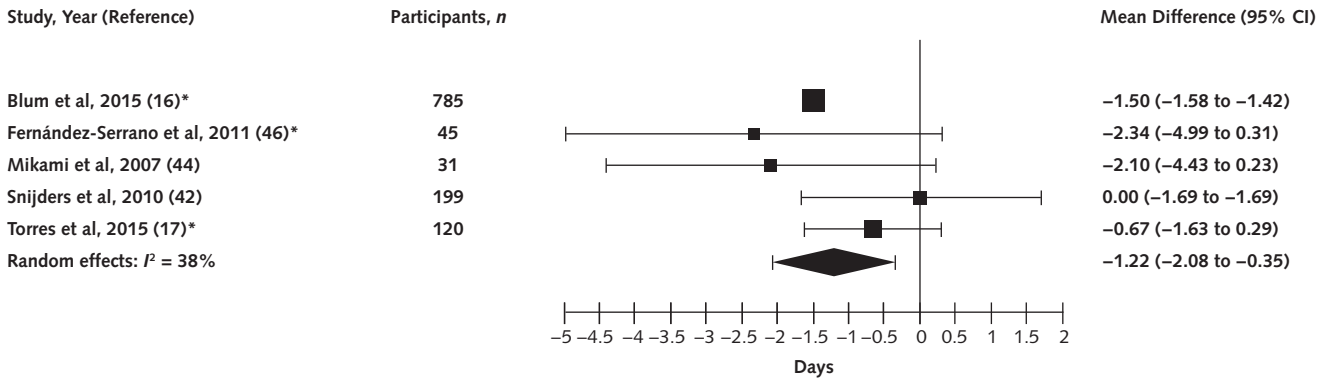
See Figure 4 for the primary analysis.
* Reported as medians with nonparametric measures of distribution.

Appendix Table 11. Sensitivity Analyses Using Author-Reported Medians and Distributions in the 5 Studies That Reported Nonparametric Data Rather Than Conversion to Means

Analysis	Studies, *n*	Mean Difference (95% CI), *d*	*P* Value*
All studies	9	−2.80 (−5.20 to −0.41)	0.92
All studies, low risk of bias	3	−1.00 (−1.61 to −0.39)	1
Reported median	5	−0.94 (−3.64 to 1.76)	0.97
Reported median, low risk of bias	2	−1.00 (−1.00 to −1.00)	1

* *P* value vs. equivalent primary analysis with conversion to parametric data, most in Appendix Table 10.

Appendix Figure 7. Change in time to clinical stability associated with adjunctive corticosteroid therapy in patients with community-acquired pneumonia.



* Parametric data estimated from nonparametric data reported in the primary study.

Appendix Table 12. Subgroup Analyses for Mean Change in Time to Clinical Stability Associated With Adjunctive Corticosteroid Use for Patients Hospitalized With CAP

Subgroup, by Analysis	Studies, *n*	Mean Difference (95% CI), *d*	*P* Value
Risk of bias			
Low	3	−1.26 (−3.06 to 0.54)	
High	2	−0.97 (−9.03 to 7.09)	0.95
Year			
≤2000	0	-	
≥2001	5	-	-
Severity			
Severe	1	−0.67 (−1.63 to 0.29)	
Not severe	4	−1.41 (−2.55 to −0.27)	0.33
Prescription duration			
≤3 d	1	−2.10 (−4.43 to 0.23)	
≥4 d	4	−1.12 (−2.00 to −0.24)	0.44
Estimated from medians			
Reported mean	2	−0.89 (−13.84 to 12.06)	
Reported median	3	−1.33 (−2.71 to 0.05)	0.95

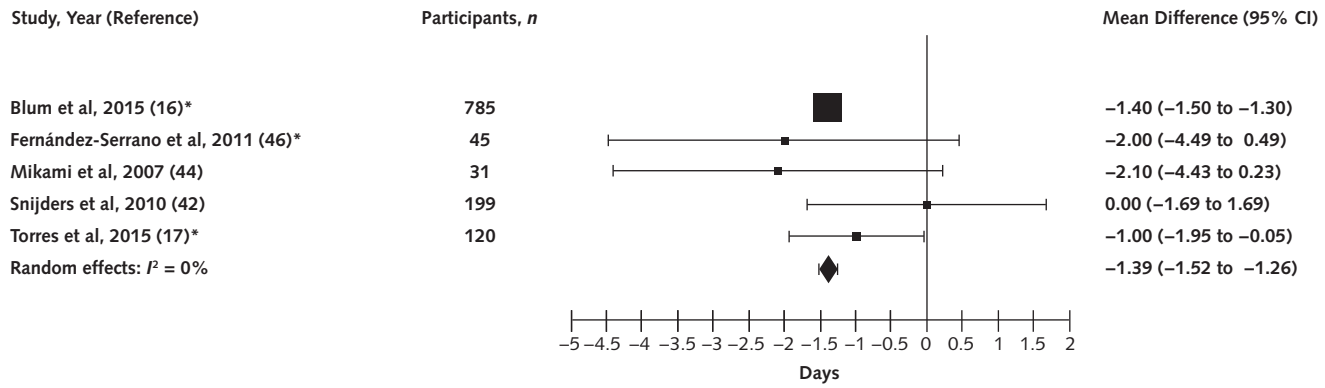
CAP = community-acquired pneumonia.

Appendix Table 13. Sensitivity Analyses Using Reported Medians and Distributions in the 3 Studies That Reported Nonparametric Data Rather Than Conversion for Time to Clinical Stability

Analysis	Studies, *n*	Mean Difference (95% CI), *d*	*P* Value*
All studies	5	−1.39 (−1.52 to −1.26)	0.70
Reported median	3	−1.40 (−1.55 to −1.25)	0.92

* *P* value vs. equivalent primary analysis with conversion to parametric data.

Appendix Figure 8. Time to clinical stability: sensitivity analysis with reported medians instead of imputed means.



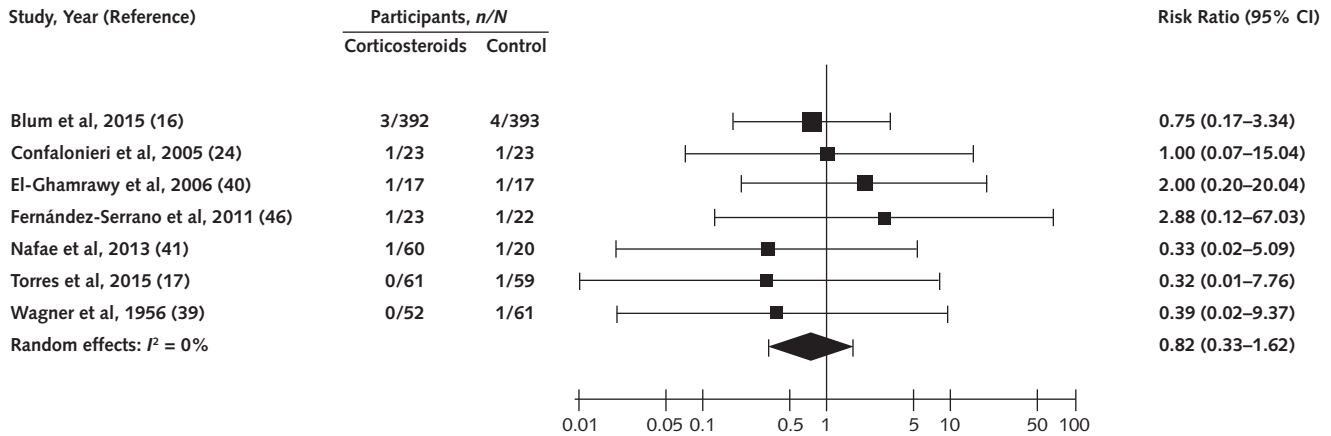
See Figure 4 for the primary analysis.
* Reported as medians with nonparametric measures of distribution.

Appendix Table 14. Subgroup Analyses for Risk for Hyperglycemia Associated With Adjunctive Corticosteroid Therapy for Patients Hospitalized With CAP

Subgroup, by Analysis	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	3	1.77 (1.25–2.51)	
High	3	1.03 (0.35–3.06)	0.35
Year			
≤2000	0	–	
≥2001	6	–	–
Severity			
Severe	2	1.03 (0.02–56.51)	
Not severe	4	1.78 (1.40–2.26)	0.79
Prescription duration			
≤3 d	0	–	
≥4 d	6	–	–

CAP = community-acquired pneumonia; RR = risk ratio.

Appendix Figure 9. Gastrointestinal hemorrhage associated with adjunctive corticosteroid therapy in patients with community-acquired pneumonia.

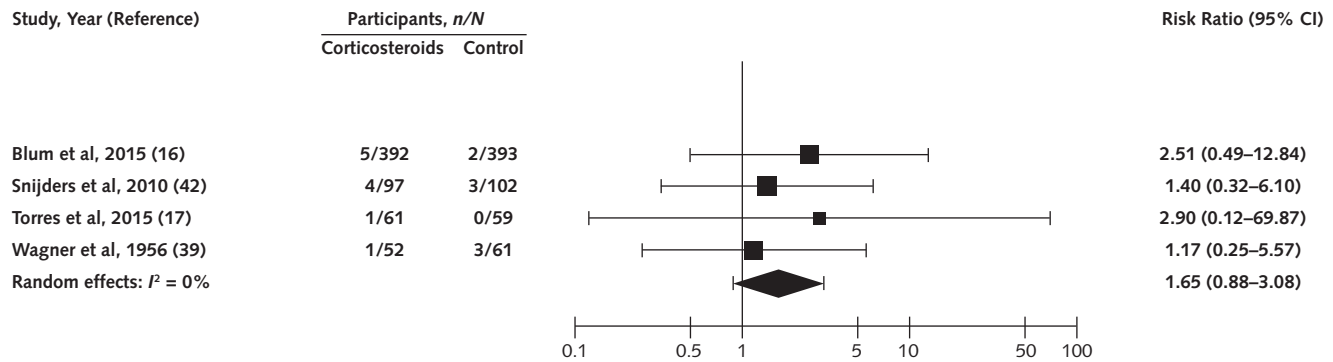


Appendix Table 15. Subgroup Analyses for Gastrointestinal Hemorrhage Associated With Adjunctive Corticosteroid Therapy in Patients Hospitalized With CAP

Subgroup, by Analysis	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	1	0.75 (0.17–3.34)	
High	6	0.86 (0.32–2.32)	0.88
Year			
≤2000	1	0.39 (0.02–9.37)	
≥2001	6	0.82 (0.37–1.80)	0.65
Severity			
Severe	4	0.62 (0.13–2.86)	
Not severe	3	0.84 (0.15–4.86)	0.80
Prescription duration			
≤3 d	0	–	
≥4 d	7	–	–

CAP = community-acquired pneumonia; RR = risk ratio.

Appendix Figure 10. Severe neuropsychiatric complications associated with adjunctive corticosteroid therapy in patients with community-acquired pneumonia.



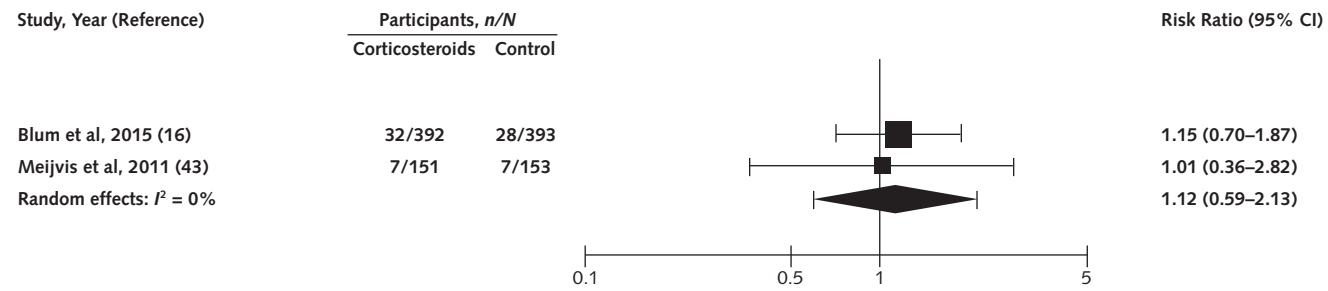
Severe neuropsychiatric complications include but are not limited to mania, psychosis, and delirium.

Appendix Table 16. Subgroup Analyses for Neuropsychiatric Complications Associated With Adjunctive Corticosteroid Therapy in Patients Hospitalized With CAP

Subgroup	Studies, *n*	RR (95% CI)	*P* Value
Risk of bias			
Low	2	1.82 (0.05–71.45)	
High	2	1.40 (0.01–131.27)	0.93
Year			
≤2000	1	1.17 (0.25–5.57)	
≥2001	3	1.91 (0.75–4.88)	0.60
Severity			
Severe	1	2.90 (0.12–69.87)	
Not severe	3	1.82 (0.64–5.21)	0.79
Prescription duration			
≤3 d	0	–	
≥4 d	4	–	–

CAP = community-acquired pneumonia; RR = risk ratio.

Appendix Figure 11. Risk for rehospitalization after discharge with adjunctive corticosteroid therapy for patients hospitalized with community-acquired pneumonia.



Appendix Table 17. OIS Calculations for Selected Outcomes in Corticosteroids for CAP*

Outcome	Control Event Rate	Calculated RR	Predicted RRR	OIS, *n*	Actual Size, *n*
Mortality	7.9%	0.67	30%	3500	1974
Mechanical ventilation†	5.7%	0.45	30%	4948	1060
ICU admission†	7.6%	0.69	30%	3648	950
ARDS†	3.0%	0.24	30%	9630	945
Duration of hospitalization	*n*-adjusted median SD = (2.24)	Mean difference = −1.00	1-d reduction	80	1499
Time to clinical stability	*n*-adjusted median SD = (0.74)	Mean difference = −1.22	1-d reduction	10	1180
Hyperglycemia	7.7%	1.49	+30%	4748	1534
Gastrointestinal hemorrhage†	1.5%	0.82	+20%	56 608	1223
Severe neuropsychiatric complications†	1.3%	1.69	+20%	65 462	1217

ARDS = acute respiratory distress syndrome; CAP = community-acquired pneumonia; ICU = intensive care unit; OIS = optimal information size; RR = risk ratio; RRR = relative risk reduction.
* α error = 0.05; β = 0.80.
† Rated down for imprecision.

Corticosteroids for Severe Community-Acquired Pneumonia: Time to Change Clinical Practice

> Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.
>
> –Sir William Osler

Community-acquired pneumonia (CAP) is a leading cause of hospitalization, morbidity, and mortality (1, 2). Systemic adjunctive corticosteroid therapy in patients with CAP has been shown to affect local and systemic inflammatory response (3) and may decrease the frequency of the acute respiratory distress syndrome (ARDS), sepsis, and mortality, but its use is controversial (4). Over the past decade, several randomized, controlled trials have evaluated the effect of short-term administration of systemic corticosteroid therapy in patients with CAP. Some of these trials showed a reduction in mortality in the group treated with corticosteroids (possibly due to modulation of systemic inflammatory response) and statistically significant improvement in clinical end points, including radiographic appearance, severity of the multiple organ dysfunction syndrome, oxygenation (PaO_2–FIO_2 ratio), and duration of intensive care unit and hospital stay (5). However, other trials showed no differences in 30-day mortality, time to clinical stability, or length of hospital stay. Furthermore, these studies suggested that late clinical failure (>72 hours from admission) was more common in the corticosteroid group (6). Given the variability in results and in CAP severity, systematic evaluation and synthesis of all available evidence are needed to better understand the effectiveness of adjunctive corticosteroid therapy in hospitalized patients with CAP.

We applaud Siemieniuk and colleagues for their systematic review and meta-analysis of 13 randomized, controlled trials of hospitalized patients with CAP (total $n = 2005$) who received systemic corticosteroid therapy or placebo (7). The authors applied pneumonia severity scores based on commonly used criteria; excluded clinical studies limited to patients with chronic obstructive pulmonary disease; and assessed the evidence using the Grading of Recommendations Assessment, Development, and Evaluation system. The analysis showed that the use of systemic corticosteroid therapy in patients with CAP is associated with reductions in mechanical ventilation and development of ARDS (moderate certainty) and reductions in time to clinical stability and duration of hospitalization (high certainty). The review also showed a possible reduction in mortality, but this effect was observed primarily in the subgroup of patients with severe pneumonia. Although the studies included in this analysis generally excluded patients at high risk for adverse effects from corticosteroids, those receiving therapy had an increased risk for hyperglycemia.

The authors noted that the included studies used various agents, routes of administration, and doses. These factors will need to be disentangled in future well-designed, randomized, controlled trials. The ESCAPe (Extended Steroid in CAP[e]) study, sponsored by the U.S. Department of Veterans Affairs (Clinical Trials.gov: NCT01283009), is such a trial. Hospitalized patients with CAP are being randomly assigned in a 1:1 ratio to receive methylprednisolone (7 days of a full dose [40 mg/d], 7 days of a half dose [20 mg/d], and 6 days of tapering doses [12 and 4 mg/d]) or placebo in a double-blind fashion. The objective of this study is to evaluate the effects of prolonged systemic corticosteroid therapy on short- and long-term mortality and morbidity in patients hospitalized with severe CAP. The investigators are also evaluating clinical failure and other end points. Clinical studies such as this are pivotal to defining which agent to use, at what dose, and for how long.

Given the results of Siemieniuk and colleagues' review, what should clinicians do when treating patients hospitalized with severe CAP? We believe that this meta-analysis supports the use of systemic corticosteroid therapy in such patients, but who are they? Obviously, severe CAP is present in those requiring mechanical ventilation, vasopressors, or both, but only one third of hospitalized patients with CAP need these interventions. We advocate the use of biomarkers, such as C-reactive protein levels, as indicators of the degree of systemic inflammation. In CAP, elevated serum C-reactive protein levels are associated with higher rates of treatment failure (8) and mortality (9). A recent study randomly assigned hospitalized patients with CAP to receive systemic corticosteroid therapy or placebo if they had an elevated C-reactive protein level (>15 mg/L) (10). Corticosteroids resulted in a statistically significant decrease in treatment failure but no change in mortality. We believe that future clinical studies must take into consideration host inflammatory response; potential interactions with other treatments, such as macrolides; and other end points in addition to mortality, such as clinical failure. Clinical failure could be defined by need for mechanical ventilation, development of hemodynamic shock, use of vasopressors, radiographic progression, or persistent respiratory failure. As clinicians, we need to balance the benefits and harms of systemic corticosteroid therapy to provide optimal care for patients with severe CAP.

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References

1. **DeFrances CJ, Lucas CA, Buie VC, Golosinskiy A.** 2006 National Hospital Discharge Survey. Natl Health Stat Report. 2008:1-20.
2. **Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al; CDC EPIC Study Team.** Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015. [PMID: 26172429]
3. **Montón C, Ewig S, Torres A, El-Ebiary M, Filella X, Rañó A, et al.** Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study. Eur Respir J. 1999;14:218-20. [PMID: 10489855]
4. **Sibila O, Ferrer M, Agustí C, Torres A.** Corticosteroids as adjunctive treatment in community-acquired pneumonia. Minerva Anestesiol. 2014;80:1336-44. [PMID: 24518215]
5. **Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al.** Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. Am J Respir Crit Care Med. 2005;171:242-8. [PMID: 15557131]
6. **Snijders D, Daniels JM, de Graaff CS, van der Werf TS, Boersma WG.** Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. Am J Respir Crit Care Med. 2010;181:975-82. [PMID: 20133929] doi:10.1164/rccm.200905-0808OC
7. **Siemieniuk RAC, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, et al.** Corticosteroid therapy for patients hospitalized with community-acquired pneumonia. A systematic review and meta-analysis. Ann Intern Med. 2015;163:519-28. doi:10.7326/M15-0715
8. **Menéndez R, Martínez R, Reyes S, Mensa J, Filella X, Marcos MA, et al.** Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. Thorax. 2009;64:587-91. [PMID: 19131448] doi:10.1136/thx.2008.105312
9. **Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT.** Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2012;186:657-65. [PMID: 22744718] doi:10.1164/rccm.201203-0487OC
10. **Torres A, Sibila O, Ferrer M, Polverino E, Menendez R, Mensa J, et al.** Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. JAMA. 2015;313:677-86. [PMID: 25688779] doi:10.1001/jama.2015.88

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