Effect of Corticosteroids on Mortality and Clinical Cure in Community-Acquired Pneumonia A Systematic Review, Meta-analysis, and Metaregression of Randomized Control Trials

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BACKGROUND: Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality. Corticosteroids may be a beneficial adjunct in the treatment of bacterial pneumonia.
RESEARCH QUESTION: Is there any benefit of corticosteroid therapy in the management of bacterial CAP among patients requiring hospitalization?
STUDY DESIGN AND METHODS: PubMed, Cochrane Library, and Embase were searched to identify randomized controlled trials assessing the use of systemic corticosteroids compared with standard care in the management of CAP. A systematic review, meta-analysis, and Trial Sequential Analysis (TSA) were performed. The primary outcome was all-cause mortality. Secondary outcomes included ICU admission, mechanical ventilation, treatment failure, readmission, and adverse events. Data are presented as relative risk (RR) with 95% CI, P value, heterogeneity (I2), and TSA-adjusted CIs.
RESULTS: Sixteen trials met the eligibility criteria. All-cause mortality (16 studies [3,842 patients]; RR, 0.85 [95% CI, 0.67-1.07]; P ¼ .17; I2 ¼ 14%; TSA-adjusted CI, 0.61-1.09), ICU admission (six studies [2,619 patients]; RR, 0.66 [95% CI, 0.45-0.97]; P ¼ .04; I2 ¼ 0%; TSA-adjusted CI, 0.37-1.12), treatment failure (six studies [2,093 patients]; RR, 0.78 [95% CI, 0.37-1.67]; P ¼ .52; I2 ¼ 68%; TSA-adjusted CI, 0.02-25.5), and the incidence of adverse events (six studies [2,487 patients]; RR, 1.10 [95% CI, 0.97-1.25]; P ¼ .14; I2 ¼ 53%; TSA-adjusted CI, 0.82-2.41) were similar between patients receiving corticosteroids and patients assigned to the control group. The need for mechanical ventilation (eight studies [1,457 patients]; RR, 0.51 [95% CI, 0.33-0.77]; P ¼ .001; I2 ¼ 0%; TSA-adjusted CI, 0.20-0.85) was lower among patients receiving corticosteroids compared with those receiving standard care. However, corticosteroid use may be associated with higher rates of hospital readmission (five studies [2,853 patients]; RR, 1.20 [95% CI, 1.05-1.38]; P ¼ .008; I2 ¼ 0%; TSA-adjusted CI, 0.89-1.98).

INTERPRETATION: Corticosteroid therapy is associated with a lower incidence of progression to requiring mechanical ventilation among patients hospitalized with CAP. No association was found between corticosteroid therapy and mortality, treatment failure, or adverse events.
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KEY WORDS: bacterial pneumonia; community-acquired pneumonia; corticosteroids; meta-analysis; steroids

Take-home Points

Study question: Is there any clinical benefit of adjuvant corticosteroid therapy in the management of bacterial community-acquired pneumonia (CAP) among patients requiring hospitalization?

Results: Sixteen trials met the eligibility criteria. All-cause mortality (16 studies [3,842 patients]; relative risk [RR], 0.85 [95% CI, 0.67-1.07]; P ¼ .17; I2 ¼ 14%; TSA-adjusted CI, 0.61-1.09), ICU admission (six studies [2,619 patients]; RR, 0.66 [95% CI, 0.45-0.97]; P ¼ .04; I2 ¼ 0%; TSA-adjusted CI, 0.37-1.12), treatment failure (six studies [2,093 patients]; RR, 0.78 [95% CI, 0.37-1.67]; P ¼ .52; I2 ¼ 68%; TSA-adjusted CI, 0.02-25.5), and the incidence of adverse events (six studies [2,487 patients]; RR, 1.10 [95% CI, 0.97-1.25]; P ¼ .14; I2 ¼ 53%; TSA-adjusted CI, 0.82-2.41) were similar between patients receiving corticosteroids and patients assigned to the control group. The need for mechanical ventilation (eight studies [1,457 patients]; RR, 0.51 [95% CI, 0.33-0.77]; P ¼ .001; I2 ¼ 0%; TSA-adjusted CI, 0.20-0.85) was lower among patients receiving corticosteroids compared with those receiving standard care. How-ever, corticosteroid use may be associated with higher rates of hospital readmission (five studies [2,853 patients]; RR, 1.20 [95% CI, 1.05-1.38]; P ¼ .008; I2 ¼ 0%; TSA-adjusted CI, 0.89-1.98).

Interpretation: Corticosteroid therapy is associated with a lower incidence of progression to requiring mechanical ventilation among patients hospitalized with CAP. No association was found between corticosteroid therapy and mortality, treatment failure, or adverse events.

Community-acquired bacterial pneumonia is a leading cause of hospitalization, with a significant risk of mortality and morbidity.1 Apart from antimicrobial therapy, no routinely

used therapeutic strategies are associated with improvements in illness mortality, severity, or hospital stay. Corticosteroids are used as adjunctive therapy in several infectious diseases, including bacterial meningitis, Pneumocystis pneumonia, TB, and septic shock.2,3 More recently, use has been recommended for patients hospitalized with COVID-19 pneumonia.4,5 Corticosteroids are considered to ameliorate the host inflammatory response and, in doing so, may reduce systemic inflammation and associated organ dysfunction.6 They also may reduce vascular hyporeactivity in septic shock by lowering vasopressor requirements.7 However, the potential benefit of adjunctive corticosteroid use in pneumonia is inconclusive.8 Current UK guidelines state that "steroids are not routinely recommended for the management of high severity community-acquired pneumonia" (CAP).9,10 In contrast, South African guidelines recommend that "the use of systematic corticosteroids should be considered along with standard care in patients with severe community-acquired pneumonia requiring admission in intensive care units."11 We performed an up-to-date systematic review and meta-analysis of randomized controlled trials assessing the effectiveness and safety of systemic corticosteroid adjuvant therapy in community-acquired bacterial pneumonia among hospitalized patients.

Study Design and Methods

International Prospective Register of Systematic Reviews Registration

This review was registered with the International Prospective Register of Systematic Reviews (Identifier: CRD42021279359) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (e-Appendix 1).

Eligibility Criteria

All randomized controlled trials evaluating the use of adjunctive systemic corticosteroids compared with standard of care regarding mortality among adult patients hospitalized with CAP were considered. Inclusion and exclusion criteria were determined a priori. We excluded trials including pediatric populations or corticosteroid therapy in both the intervention and the control groups. Only full-text articles were considered.

Primary Outcomes

All cause-mortality was selected as the primary outcome. We assessed the association between steroid use and all-cause mortality. Because steroid therapy may affect the patients with the greatest illness severity, we conducted a metaregression to explore the association between baseline risk of mortality (as a surrogate of illness severity) and the effect of steroids. To explore further the association among steroid dosing strategies, we performed a metaregression to explore the associations between the dose of steroid, duration of steroid treatment, and average daily dose of steroid and mortality. Doses of different steroid classes were converted to daily hydrocortisone equivalent doses.

Secondary Outcomes

Secondary outcomes included progression to severe disease defined as either a requirement for mechanical ventilation, ICU admission, or a composite. Treatment failure was defined as the lack of improvement in clinical signs and symptoms or radiographic progression after systemic corticosteroid administration. Readmission was defined as a first improvement or resolution of clinical signs and symptoms after completion of treatment, followed by a recurrence requiring rehospitalization. Adverse events included the total number of adverse events or the total number of patients experiencing any adverse event associated with corticosteroid use. Data on steroid-associated adverse events included the incidence of secondary infections, GI bleeding, and hyperglycemia.

Information Source and Search Strategy

A systematic search was conducted in PubMed, Cochrane Library, and Embase using a controlled vocabulary (medical subject headings) and key words. Additionally, we reviewed relevant references of included studies and conference proceedings. Date and language restrictions were not applied. The last search update was performed on June 27, 2022. The Boolean search strategy was as follows: ((pneumonia OR lower respiratory chest infection OR LRTI [lower respiratory tract infection] OR chest infection) AND (steroid OR corticoid OR prednisolone OR hydrocortisone OR dexamethasone OR solumedrone) AND (clinical trial OR randomized controlled trial or controlled trial) NOT (COVID OR viral)). The control group and outcomes were not defined in search terms to maximize the scope of relevant articles. Research articles and review articles were hand searched for further relevant trials. We

reviewed trials included in recent systematic reviews assessing steroids for CAP for inclusion eligibility.

Study Selection

Two investigators (N. S., A. K.) independently screened titles and abstracts. Discrepancies about the selection of studies for the current review were resolved by a third author (N. A.). Relevant full-text articles were retrieved and analyzed for selection by using the predefined inclusion criteria.

Data Extraction and Analysis

Two investigators (N. S., A. K.) independently extracted information from selected studies. Data extraction was performed using a standardized data collection form. Data collected included study name, country of trial, recruitment period, the total number of participants, corticosteroid type, dosage and duration, hydrocortisone mean equivalence, and the number of patients hospitalized with CAP receiving systemic corticosteroids in addition to antibiotics at the time of enrolment. The following data points were collected for patients in each treatment arm: all cause-mortality, disease progression (ICU admission or mechanical ventilation), treatment failure, hospital readmission, and adverse events. Where both intention-to-treat and per-protocol analysis were reported, we used intention-to-treat data for analysis.

Risk-of-Bias Assessment

To assess the methodologic quality of the included randomized control trials, the Cochrane Collaboration tool for assessing the risk of bias, RoB2, was used.12 This assessment was performed independently by two authors (N. S., A. K.); any discrepancies regarding study selection were reconciled by a third author (T. A. C. S.). The risk of bias assessment included the following domains: random sequence generation, allocation concealment, masking of participants and personnel, masking of the outcome, incomplete outcome data, selective reporting, and other biases. The risk of bias in each domain was classified as either low, high, or unclear.

Grading the Quality of Evidence

The quality of evidence for each outcome measure was assessed following the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADEpro Guideline Development Tool; McMaster University).13 Quality was downgraded based on the following certainty assessments: risk of bias, inconsistency, indirectness, imprecision, and other considerations. The overall quality of evidence subsequently was rated as very low, low, moderate, or high.

Data Synthesis and Analysis

Data synthesis for this meta-analysis was performed using Review Manager version 5.4 (The Cochrane Collaboration). Data on dichotomous outcomes are presented as risk ratios (RRs), 95% CIs, and P values. A random-effects model with the generic Mantel-Haenszel method was preferred for integrating RRs. All P values were two-tailed and were considered statistically significant if < .05.

The I2 method was used to assess the magnitude of variation secondary to heterogeneity. Heterogeneity between studies was evaluated graphically as a forest plot plus the I2 statistic whereby I2 = 0% indicates minimal heterogeneity, 0% < I2 < 30% indicates least heterogeneity, 30% # I2 < 50% indicates moderate heterogeneity, 50% # I2 < 75% indicates substantial heterogeneity, and I2 > 75% indicates considerable heterogeneity. Publication bias was investigated using a funnel plot and Harbord's test.

Because type I errors may occur in meta-analyses with sample sizes that are too small, a Trial Sequential Analysis (TSA) was performed using TSA program version 0.9.5.10 (Copenhagen Trial Unit). The TSA tests the credibility of the meta-analysis results by combining an estimation of the required information size calculated from the cumulative sample size of included trials, with an adjusted threshold for statistical significance. Meta-analysis monitoring boundaries (trial sequential monitoring boundaries) and the required information size were quantified, alongside diversity-adjusted information size and adjusted 95% CIs. Diversity adjustment was performed according to an overall type I error of 5% and power of 80%. To demonstrate the efficacy and safety of adjunctive corticosteroid therapy in addition to standard care for the treatment of CAP, required information size was calculated using an RR reduction of 35.4% based on results from previous meta-analyses

assessing the effectiveness and safety of adjuvant corticosteroid therapy for patients with CAP.[14]

Meta-regression was used to investigate the effect of overall risk (using the control group event rate), cumulative dose, and duration of steroids using a random-effects model in Stata version 17 software (StataCorp).

Results

Search Strategy

The search strategy identified 7,400 results. After the removal of duplicates, 6,021 articles remained. Of these 6,021 articles, 5,999 were excluded based on title or abstract. Of the remaining 22 studies, six were excluded after full-text review because they included a pediatric population15-19 or because of overlapping data.20 Sixteen trials were selected for final analysis and review (Fig 1).21-36

Trial Characteristics

Among the 16 trials, 3,863 patients were enrolled, with mortality reported in 3,842 patients. Among the 3,842 patients with mortality outcomes reported, 1,910 patients (49.4%) were allocated to receive systemic corticosteroids (Table 1,e-Table 1).21-36 Seven trials included adults with severe CAP.23-25,28,29,33,36 Five trials24,25,28,33,36 defined severe pneumonia according to the Infectious Diseases Society of America and American Thoracic Society guidelines.37 Marik et al23 defined severe pneumonia using the British Thoracic Society criteria for severe pneumonia.38 Fernández-Serrano et al29 defined pneumonia as the presence of respiratory failure and extensive radiologically confirmed consolidation. Corticosteroid regimens included oral dexamethasone in one trial,35 oral prednisone in two trials,22,32 IV prednisolone in two trials,26,34 IV dexamethasone in one trial,30 IV hydrocortisone in six trials,21,23-25,28,31 and IV methylprednisolone in three trials.29,33,36 One trial used prednisone without specifying the administration route.27

The duration of corticosteroid treatment varied from 20 days in one trial36 to 10 days in another trial,29 7 days in eight trials,22,24,25,27,28,31,32,34 5 days in two trials,21,33 and 2 to 4 days in three trials.26,30,35 One study administered a single dose of corticosteroid.23

Primary Outcome: All-Cause Mortality

All 16 studies identified reported all-cause mortality.21-36 Mortality rates in the control group ranged from 0% to 35% with an overall mortality of 10.2%. No significant difference was found in mortality between patients receiving adjuvant corticosteroid therapy compared with standard care (9.5% vs 10.8%; RR, 0.85 [95% CI, 0.67-1.07]; P ¼ .17; I2 ¼ 14%; TSA-adjusted CI, 0.61-1.09)(Fig 2). The cumulative z curve crossed neither the conventional nor the TSA boundary for benefit or harm, but did cross the boundary for futility having exceeded the required information size (Fig 3).

Meta-regression analysis provided evidence of an association between the effect of corticosteroids on the reduction of mortality and the baseline risk of mortality (P ¼ .04) (e-Fig 1). No evidence was found that a higher average daily dose of corticosteroids was associated with lower mortality (P ¼ .13). Similarly, no evidence was found of a univariate association between the effect of corticosteroids and either cumulative dose (P ¼ .68) or duration of treatment (P ¼ .62).

Secondary Outcomes: Need for ICU Admission or Mechanical Ventilation

Six studies including 2,619 patients reported data on the need for ICU admission after randomization.27,29,30,32,34,35 Patients receiving adjunctive corticosteroids showed a lower risk of ICU admission compared with those receiving standard care alone (3.1% vs 4.7%; RR, 0.66 [95% CI, 0.45-0.97]; P ¼ .04; I2 ¼ 0%; TSA-adjusted CI, 0.37-1.12) (Fig 4A). Among these six studies, corticosteroid use was not associated with a reduction in mortality (8.6% vs 8.2%; RR, 1.07 [95% CI, 0.83-1.37]; P ¼ .61; I2 ¼ 0%) (e-Fig 2A).27,29,30,32,34,35 Eight studies including 1,457 patients reported data on the need for mechanical ventilation after randomization.23,24,27-29,31,33,34 Patients receiving adjunctive corticosteroids showed a lower risk of requiring ventilation compared with those receiving standard care alone (4.2% vs 7.1%; RR, 0.51 [95% CI, 0.33-0.77]; P ¼ .001; I2 ¼ 0%; TSA-adjusted CI, 0.20-0.85) (Fig 4B). Among these eight studies, corticosteroid use was not associated with a

reduction in mortality (12.3% vs 14.3%; RR, 0.61 [95% CI, 0.34-1.09]; P ¼ .09; I2 ¼ 50%) (e-Fig 2B).

Treatment Failure and Hospital Readmission

Six trials including 2,093 patients reported the incidence of treatment failure.24,27,28,32-34 No statistically significant difference was found in treatment failure between patients receiving adjunctive corticosteroids and those receiving standard care alone (5.3% vs 5.7%; RR, 0.78; 95% CI, 0.37-1.67; P ¼ .52; I2 ¼ 68%; TSA-adjusted CI, 0.02-25.5) (e-Fig 3A).

Hospital readmission rate was reported in five trials including 2,853 patients.30,32,34-36 Hospital readmission was higher among patients receiving corticosteroid therapy compared with patients who did not (21.5% vs 17.7%; RR, 1.20 [95% CI, 1.05-1.38]; P ¼ .008; I2 ¼ 0%; TSA-adjusted CI, 0.89-1.98) (e-Fig 3B).

Adverse Events

Adverse events were reported in six trials including 2,487 patients, of whom 1,212 received adjuvant corticosteroids.21-23,32,34,36 Overall, 27.2% of patients were reported to have experienced at least one adverse event associated with corticosteroid use. Systemic corticosteroid therapy was not associated with an increased risk of total adverse events compared with standard care (55.8% vs 48.5%; RR, 1.10 [95% CI, 0.97-1.25]; P ¼ .14; I2 ¼ 53%; TSA-adjusted CI, 0.82-2.41) (e-Table 2, e-Fig 4A).

Hyperglycemia was reported in nine trials.27,29-36 Corticosteroid use was associated with an increased incidence of new-onset hyperglycemic events compared with standard care (17.6% vs 9.5%; RR, 1.68 [95% CI, 1.30-2.16]; P ¼ .0001; I2 ¼ 37%; TSA-adjusted CI, 1.30-3.83) (e-Fig 4B). No increased risk of GI bleeding (reported in 10 trials) was found (RR, 1.46 [95% CI, 0.81-2.61]; P ¼ .21; I2 ¼ 0%; TSA-adjusted CI, 0.20-8.38) (e-Fig 4C),24,25,28-34,36 nor was one found for secondary infections (reported in eight trials; RR, 1.19 [95% CI, 0.62-2.28]; P ¼ .59; I2 ¼ 54%; TSA-adjusted CI, 0.26-4.82) (e-Fig 4D)24,25,27,28,30,32,33,36 among patients receiving corticosteroid therapy compared with those receiving standard care.

Sensitivity Analyses

A sensitivity analysis performed on the primary outcome of all-cause mortality using a fixed-effects model revealed no mortality benefit associated with adjuvant corticosteroid therapy compared with standard care in the management of CAP in hospitalized patients (9.5% vs 10.8%; RR, 0.88 [95% CI, 0.73-1.06]; P ¼ .17; I2 ¼ 14%; TSA-adjusted CI, 0.66-1.13) (e-Fig 5A). Seven trials (including 2,490 patients) were deemed to have a low Rob2 score.24,27,30,33-36 Therefore, an additional analysis was performed by using a random-effects model, demonstrating no mortality benefits with adjuvant corticosteroid therapy (12% vs 13%; RR, 0.94 [95% CI, 0.73-1.20]; P ¼ .60; I2 ¼ 14%; TSA-adjusted CI, 0.64-1.27) (e-Fig 5B).

Risk of Bias and Grade Recommendation

Nine of 16 trials (56.2%) were sponsored by a pharmaceutical company.22,23,27,29,32-36 Four were open-label studies,22,23,26,31 whereas 11 studies were double-masked, lowering the risk of performance bias (e-Table 3).24,25,27-30,32-36 Inconsistency in reporting different secondary outcomes was deemed serious because of substantial (> 50%) heterogeneity in reporting. Indirectness was deemed not serious. Imprecision was judged as not serious in all domains because of the availability of lesser numbers of participants in selected studies. Evidence was found of publication bias considering the asymmetry in the funnel plot (P ¼ .016, Harbord test) (e-Fig 6). The overall quality of evidence on the Grading of Recommendations Assessment, Development, and Evaluation assessment was very low (Table 3).

Discussion

The efficacy and safety of adjunctive corticosteroid therapy in the management of patients hospitalized with bacterial pneumonia have been controversial. In this up-to-date meta-analysis, comprising 16 studies and 3,842 patients, no association was found between corticosteroid use and mortality. However, adjuvant corticosteroids may be associated with a reduction in disease progression, that is, the need for mechanical ventilation. The reduction in the requirement for mechanical ventilation associated with corticosteroid use in CAP did not translate to a reduction in mortality, although the TSA suggests that more trial data are required.

Severe CAP is associated with the release of pathogen-and damage-associated molecular patterns resulting in inflammation and organ dysfunction. The inflammatory response may

be ameliorated using systemic corticosteroids, particularly in patients with greater illness severity. Indeed, among patients with ARDS, a survival benefit may associated with early corticosteroid use.39 However, patients with ARDS constitute a heterogeneous group of underlying diagnoses with significant illness severity, and direct extrapolation cannot be made to patients with CAP.

It is unknown whether stratification of patients by surrogates of inflammation (eg, the plasma level of C-reactive protein), degree of hypoxemia, or a clinical score (eg, CURB) may help to identify those patients most likely to benefit from adjunctive steroid therapy. As a corollary, the survival benefit associated with corticosteroids in the management of COVID-19-associated respiratory failure may be limited to patients with a greater degree of respiratory failure.4 It has been postulated that mortality reduction may be evident only among patients with a high risk of death,40 which we found on meta-regression.

Excessive immunosuppression and increased incidence of hyperglycemia both may increase the risk of persistent or secondary infections. Despite an increased risk of hyperglycemia associated with steroid use, we found no association between corticosteroid use and infectious complications. Corticosteroid use may be associated with an increased risk of hospital readmission, although this needs to be confirmed in further trials. The reasons for increased hospital eadmissions are not clear. Hospital readmission rates were reported only in a minority of studies, and none cited reasons for readmission. The incidence and reasons for hospital readmission need to be reported in future clinical trials. However, it was reassuring that the incidence of GI complications was not increased by corticosteroid use.

The optimal type of corticosteroid, dose, and duration are yet to be determined. Among patients with ARDS, a reduction in mortality may associated with low-dose dexamethasone.41,42 A lower-dose regimen may strike the right balance between antiinflammatory and immunosuppressive effects because higher doses used in early sepsis trials were associated with a greater risk of harm.43 We found that a higher dose of shorter duration regimen was not associated with lower mortality. The potential benefits of short-duration, high-dose steroids compared with longer duration, low-dose steroids need to be evaluated in future controlled trials. The type of corticosteroid may influence the outcome because only dexamethasone lacks any mineralocorticoid activity. The role of

mineralocorticoid activity in the progression of pulmonary hypertension is suggested by preclinical data.44

The data presented in this meta-analysis are limited to patients hospitalized with CAP of bacterial origin and do not apply to patients being managed in the community nor by ambulatory care. We were not able to adjust for any differences in diagnostic criteria, baseline illness severity, or other therapeutic interventions administered (eg, choice, duration, and route of antibiotic administration). Because corticosteroids are a relatively inexpensive and widely available therapeutic option for a common disease, their role in CAP warrants further investigation.

Interpretation

Adjuvant systemic corticosteroid therapy in patients hospitalized with bacterial pneumonia may prevent the requirement for mechanical ventilation. Larger masked randomized controlled trials are required to determine any mortality benefit, as are trials stratifying patients by illness severity. Longer-term follow-up is required because data on the incidence and causes of hospital readmission are needed. The optimal type of corticosteroid, dose, and duration are yet to be determined.

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Additional information: The e-Appendix, e-Figures, and e-Tables are available online under “Supplemental Data.”

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