REVIEWS

Corticosteroids in Community-Acquired Bacterial Pneumonia: a Systematic Review, Pairwise and Dose-Response Meta-Analysis

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ABSTRACT

INTRODUCTION: International guidelines provide heterogenous guidance on use of corticosteroids for community-acquired pneumonia (CAP).

METHODS: We performed a systematic review of randomized controlled trials examining corticosteroids in hospitalized adult patients with suspected or probable CAP. We performed a pairwise and dose-response meta-analysis using the restricted maximum likelihood (REML) heterogeneity estimator. We assessed the certainty of the evidence using GRADE methodology and the credibility of subgroups using the ICEMAN tool.

RESULTS: We identified 18 eligible studies that included 4661 patients. Corticosteroids probably reduce mortality in more severe CAP (RR 0.62 [95% CI 0.45 to 0.85]; moderate certainty) with possibly no effect in less severe CAP (RR 1.08 [95% CI 0.83 to 1.42]; low certainty). We found a non-linear dose-response relationship between corticosteroids and mortality, suggesting an optimal dose of approximately 6 mg of dexamethasone (or equivalent) for a duration of therapy of 7 days (RR 0.44 [95% 0.30 to 0.66]). Corticosteroids probably reduce the risk of requiring invasive mechanical ventilation (RR 0.56 [95% CI 0.42 to 74] and probably reduce intensive care unit (ICU) admission (RR 0.65 [95% CI 0.43 to 0.97]) (both moderate certainty). Corticosteroids may reduce the duration of hospitalization and ICU stay (both low certainty). Corticosteroids may increase the risk of hyperglycemia (RR 1.76 [95% CI 1.46 to 2.14]) (low certainty).

CONCLUSION: Moderate certainty evidence indicates that corticosteroids reduce mortality in patients with more severe CAP, the need for invasive mechanical ventilation, and ICU admission.

J Gen Intern Med 38(11):2593–606
DOI: 10.1007/s11606-023-08203-6

Received January 10, 2023
Accepted April 5, 2023
Published online April 19, 2023

INTRODUCTION

Several randomized controlled trials (RCTs) examining the role of corticosteroids in hospitalized adult patients with severe pneumonia demonstrate benefit in improving survival. This includes patients with coronavirus disease 2019 (COVID-19), and those who develop acute respiratory distress syndrome (ARDS).[1–3] Nevertheless, the adjunctive use of corticosteroids for community-acquired pneumonia (CAP) remains variable and provider dependent. International societal guidelines are heterogeneous; many recommend against the routine use of corticosteroids in patients with CAP, except in cases of refractory septic shock.[4–6] The justification against the routine use of corticosteroids includes low certainty data owing to both statistical and clinical heterogeneity, and ongoing issues with imprecision of pooled estimates. Previous analyses have been limited by few and underpowered studies, as well as a lack of analysis of optimal dosing.[7]

With the publication of a few large recent RCTs including the recent ESCAPe and CAPE COD trials examining this question, and with the objective of carefully evaluating key components of corticosteroid regimes, including dose and duration of therapy, we aimed to perform an updated systematic review and pairwise and dose-response meta-analysis of RCTs examining the role of corticosteroids in patients hospitalized with bacterial CAP.

METHODS

We generated the study protocol using the PRISMA-P guidelines and registered it on Open Science Framework: https://osf.io/nqm28.

Search Strategy

With the help of an experienced medical librarian, we developed a comprehensive search strategy (eTables 1–4). The search strategy was based on the last major review which

was first published in 2015, then updated in February 2020.[2,7] We searched Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and clinicaltrials.gov for eligible trials from February 29, 2020, to September 5, 2022. We also reviewed the results from clinicaltrials.gov for updated trial results monthly. We also reviewed previous systematic reviews addressing the topic to ensure no studies were missed.[1–3] We did not use any language restrictions and included only primary source clinical trial data. We reviewed secondary analyses and post hoc analysis for subgroup data, as required.

Eligibility Criteria

We included all RCTs that randomized adult patients (≥18 years old) hospitalized with probable or suspected CAP to treatment with corticosteroids versus standard care or placebo. We defined CAP in keeping with individual trial definitions incorporating clinical, microbiological, and/or radiographic evidence of bacterial pneumonia. We included studies of alternative doses or types of corticosteroids for the dose-response meta-analysis. If patients were hospitalized, we included all severities of disease but planned an a priori subgroup analysis based on more severe vs less severe patients. We defined trials as more severe if 50% or more of the participants had severe pneumonia scores (pneumonia severity scores of IV or V, CURB65 scores of ≥3, CORB scores of ≥2, SMART-COP scores ≥4), or if ≥50% of patients were admitted to the intensive care unit (ICU) at the time of randomization. We excluded trials that enrolled predominately (≥80%) patients with *Pneumocystis jirovecii* pneumonia, inflammatory cases of pneumonia such as organizing pneumonia, chronic obstructive pulmonary disease (COPD), COVID-19 pneumonia, other viral cases of pneumonia, empyema, post-obstructive pneumonia, or ventilator-associated pneumonia.

STUDY SELECTION AND DATA EXTRACTION

We used COVIDENCE to screen eligible trials. Two reviewers (TP, DZ), following training and calibration exercises to ensure sufficient agreement, worked independently and in duplicate to screen titles and abstracts of search records and subsequently the full texts of records that were determined potentially eligible at the title and abstract screening stage. Reviewers resolved discrepancies by discussion or, when necessary, by third-party adjudication. Similarly, the two reviewers worked independently and in duplicate to extract data from eligible trials, and resolved discrepancies by discussion or, when necessary, by third-party adjudication (BR).

We collected data on trial characteristics (author, year published, trial registration, country of enrollment), patient characteristics (age, sex, comorbidities, C-reactive protein (CRP), white blood cell (WBC) count, proportion of patients on oxygen, and proportion of patients in ICU), intervention characteristics (type of corticosteroid, dose, duration), and outcomes of interest. Outcomes of interest included mortality, need for invasive mechanical ventilation (in those not requiring invasive mechanical ventilation at baseline), secondary infections (any type and severity), gastrointestinal (GI) bleeding (defined by study authors, any severity), ICU admission (in those not requiring ICU admission at baseline), hyperglycemia (requiring intervention), and duration of ICU and hospital stay. For all dichotomous outcomes, we collected data at the longest follow-up or closest to 90 days.

For dichotomous outcomes, we extracted the number of participants analyzed and the number of events in each arm. For continuous outcomes, we collected data on the point estimate of the mean and standard deviation. When studies reported other measures of variability other than standard deviation, we converted them to standard deviations using methods proposed by Hozo et al.[8].

Risks of Bias

We rated the risk of bias at an outcome level. Two reviewers, working independently and in duplicate, assessed the risk of bias for individual RCTs using a revision of the Cochrane tool (RoB 2.0).[9–11] We rated the risk of bias as either at (i) low risk of bias, (ii) probably low risk of bias, (iii) probably high risk of bias, or (iv) high risk of bias, across the following domains: bias arising from the randomization process; departures from the intended intervention; missing outcome data; measurement of the outcome; and selection of the reported results. We classified trials rated as definitely or probably low risk of bias across domains as low risk of bias overall. We resolved discrepancies by discussion and, when necessary, with adjudication by a third party. eTable 5 presents the risk of bias tool.

Statistical Methods

Pairwise Meta-Analysis. For all outcomes, we performed a random-effects meta-analysis with the restricted maximum likelihood (REML) heterogeneity estimator.[12] We summarized the effects of interventions using relative risk (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, both with associated 95% confidence intervals (CIs). To facilitate the interpretation of dichotomous outcomes, we also calculated absolute risk differences (RD) per 1000 patients and corresponding 95% confidence intervals.[13–15] We calculated the baseline risk using the median risk in the standard care arms of the included trials.

One trial was a cluster randomized trial and therefore we calculated the associated effective sample size using the design effect as described in Cochrane guidance.[16]

Dose-Response Analysis. For mortality and adverse events found to be statistically significant, we performed an additional dose-response meta-analysis. For the dose-response analysis, we conducted a random-effects dose-response meta-analysis using the restricted maximum likelihood (REML) heterogeneity estimator and methods proposed by Greenland and colleagues[17,18] using a one-stage approach.[19] Dose-response meta-analysis estimates the association between doses of an exposure and the relative risk or mean difference of an outcome. We analyzed the cumulative dose of corticosteroids administered during the trial by multiplying the administered dose by the duration (i.e., dexamethasone 6 mg/day for 10 days = 60 mg total dose).

To address whether results are driven by cumulative exposure to corticosteroids or the duration of exposure, we performed a prespecified random-effects meta-regression and included the duration of treatment with corticosteroids as a moderator. We anticipated that if the duration of exposure rather than cumulative exposure was important, we would see larger effects in the analysis of duration rather than cumulative dose.

We used the following corticosteroid conversions: 1 mg of dexamethasone = 26.7 mg of hydrocortisone = 5.3 mg of methylprednisolone/prednisolone= 6.7 mg of prednisone.[20–22] We divided the total dose by the median number of days across trials. To ensure no differences based on molecule, we performed meta-regression using molecule as a moderator.

For analyses with five or more studies, we assessed for non-linearity by using restricted cubic splines with knots at 10%, 50%, and 90% percentiles and a Wald-type test.[23] Restricted cubic splines accommodate non-linear relationships by splitting the independent variable (i.e., dose) at "knots" and fitting separate curves between knots. For analyses in which we observed statistically significant non-linear associations, we present results from the non-linear model.

We assessed model fit by calculating deviance, adjusted and unadjusted coefficients of determination, and by decorrelated residuals-versus-exposure plot.[24] We assessed heterogeneity by inspection of forest plots, the I^2 statistic, and the chi-squared test. We considered heterogeneity ranging from 0 to 40% as potentially unimportant, 30 to 60% as moderate heterogeneity, 50 to 90% as substantial heterogeneity, and 75 to 100% as critical heterogeneity.[16] For outcomes with 10 or more studies, we tested for publication bias or small study effects using both visual inspection of funnel plots and Egger's test.[25]

For mortality, we conducted trial sequential analysis (TSA) using a random-effects model.[26] For the TSA, we used a statistical significance level of 5%, a power of 80%, and a relative risk reduction of 38%. We used a model variance-based heterogeneity correction TSA performed using Trial Sequential Analysis v.0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www. ctu.dk/tsa).

We performed all analyses using the *dosresmeta* and *meta* packages in R (version 4.03, R Foundation for Statistical Computing).[27,28] We used STATA v.17 for pairwise analyses.

A Priori Subgroup Analysis. For trials that reported on patients with less severe and more severe diseases, we extracted in-study subgroup data for outcomes of interest. When in-study subgroups were not reported, we decided on trial-level severity based on whether 50% or more of patients were categorized as severe using a validated severity score, whether patients were predominately ICU patients, or if they required vasopressors.

We performed subgroup analysis based on (1) severe CAP versus non-severe CAP, hypothesizing that those with severe disease may benefit more from corticosteroids due to a more dysregulated inflammatory response, (2) high risk of bias versus low risk of bias, hypothesizing that higher risk of bias trials would show a larger effect than the lower risk of bias trials, (3) corticosteroid type, dexamethasone versus hydrocortisone versus methylprednisolone versus prednisone/prednisolone, hypothesizing no effect, and (4) the duration of therapy (including taper), comparing trials treating for <7 days versus ≥7 days, with the hypothesis that longer duration would be more effective than shorter duration.

We assessed the credibility of statistically significant subgroups using the Instrument for Assessing the Credibility of Effect Modification Analyses (ICEMAN) tool.[29]

Certainty of the Evidence. For all outcomes, reviewers, working independently and in duplicate, assessed the certainty of the evidence using the GRADE approach.[30,31] We judged the certainty for each outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

To make judgments regarding imprecision, we used a minimally contextualized approach, which considers only whether confidence intervals include a minimally important effect and does not consider the magnitude of plausible effects, captured by confidence intervals.[32] We used a minimally important difference (MID) based on consensus of the authors. For mortality, we chose an MID of 1%, and for all other dichotomous outcomes, we chose a 2% MID. For the duration of hospitalization, ICU stay, and ventilator-free days, we chose 1 day as MID. Using updated GRADE guidance, we rated imprecision using the confidence interval method, whereby if the confidence intervals included the MID in one direction, we rated down once; if in two directions, we rated down twice.[33]

We described our results using guidance from the GRADE Working Group, based on the certainty of evidence and the magnitude of the effect (e.g., corticosteroids reduce

mortality [high certainty], corticosteroids probably reduce mortality [moderate certainty], corticosteroids may reduce mortality [low certainty], and the effect of corticosteroids on mortality is very uncertain [very low certainty]).[31]

RESULTS

Search Results

The search yielded 2666 unique citations. We identified a total of 18 eligible studies that included 4661 patients.[34–50] All trials were published in peer-reviewed journals, and all in English except for one article which was published in Mandarin (Chinese)[35]. Figure 1 presents the PRISMA flow diagram.

Trial and Participant Characteristics

Table 1 presents trial and participant characteristics. Trials recruited adult patients with a median age of 64.35 years old (interquartile range [IQR] 69.4 to 57.9). Most patients were male (70.5%) and approximately 1/3 of patients were admitted to the ICU at the time of randomization. Bacterial culture was identified in 1622 (34.8%) and 205 (4.4%) had positive viral culture or PCR (including influenza). Four-hundred and sixty-seven (10.0%) were receiving invasive mechanical ventilation, and 214 patients (4.6%) required vasopressors at randomization.

We classified ten trials as studying more severe diseases,[35–38,43,45,46,48,50] and eight as studying non-severe diseases[34,39–42,44,47,49]. Table 1 presents more details on how we categorized severity.

Of the trials that reported a pneumonia severity index (PSI), scores ranged from 89.5 to 123.9. Trials included patients who were classified with class V PSI scores ranging from 9.7 to 40%, indicating significant heterogeneity in severity across trials. The median CRP across included trials was 217 mg/L (IQR 126.9 to 254.3).

Seven trials (1178 patients) examined hydrocortisone,[36–38,43,48,49] four trials (807 patients) methylprednisolone,[35,45,46,50] five trials (1971) prednisolone/prednisone,[34,39,42,44,47] and two trials (705) examined dexamethasone.[40,41] Seven trials reported on durations of less than 7 days and two trials longer than 7 days. The median treatment duration was 7 days (IQR 5 to 7).

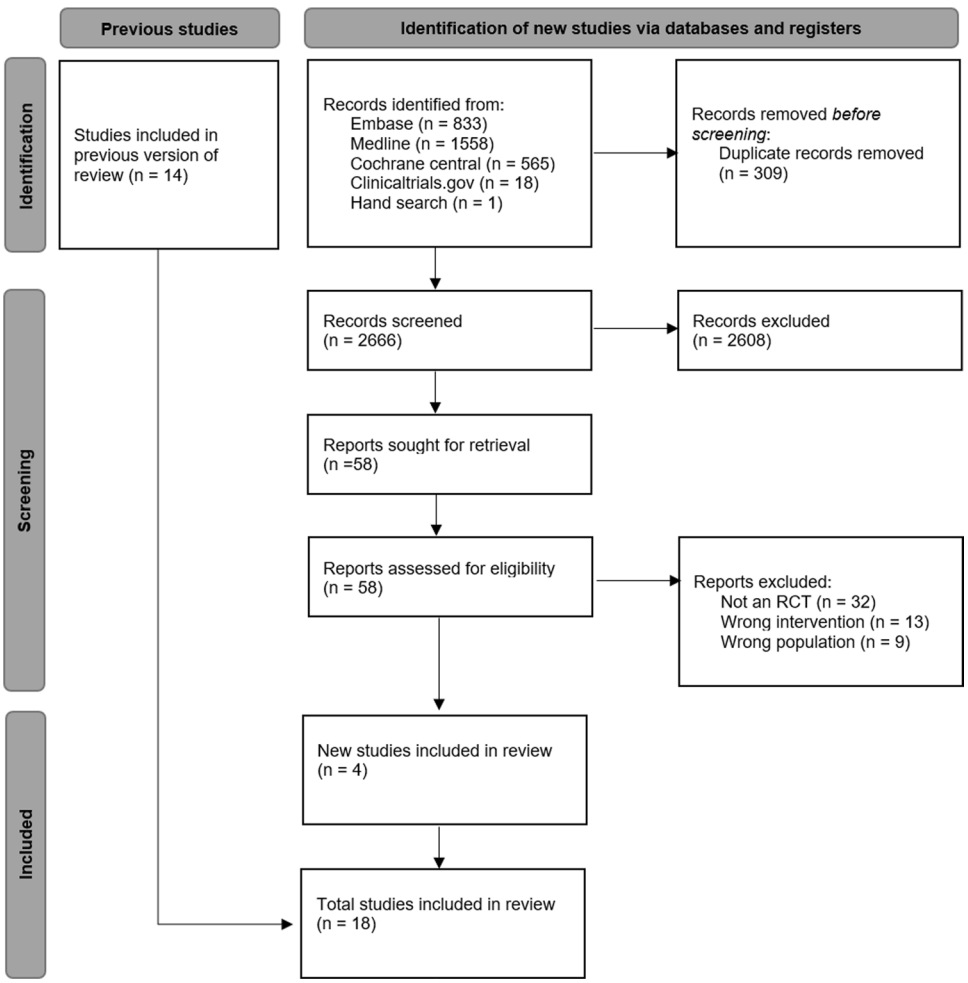

Figure 1 PRISMA flow diagram for updated systematic reviews.

Table 1 Trial Characteristics

Study	Trial registration	Country	Male (%)	Age	ICU (%)	Mechanical ventilation	Severity	CRP (mg/L)	Intervention	Number randomized
Lloyd 2019 (IMPROVe-GAP)	NCT02835040	Australia	57	76.1	10.5	NR	Non-severe [50% of patients with CORB scores <2]	88.2	Prednisone 50mg daily for 7 days	816
Gang 2016	NR	China	NR	NR	100	NR	Severe [majority ICU patients]	NR	MP 80 mg daily for 7 days	58
Nafae 2013	NR	Egypt	56.2	49	NR	0	Severe [based on baseline vitals indicating mean CORB score >2]	92.3	HCT 200 mg IV load, then 10 mg/h IV infusion for 7 days	80
Sabry 2011	NCT01228110	Egypt	72.5	62.2	100	75	Severe [majority ICU patients]	568.5	HCT 200 mg IV load, then 12.5 mg/h IV infusion for 7 days	80
Confalonieri 2005	NR	Italy	69.5	63.5	100	73.9	Severe [majority ICU patients]	420	HCT 200 mg IV load, then 10 mg/h IV infusion for 7 days	46
Mikami 2007	NR	Japan	74.2	72	0	0	Non-severe [PSI I–III >50%]	19.7	Prednisolone 40 mg IV daily for 3 days	31
Meijvis 2011 (Ovidius)	NCT00471640	Netherlands	56.5	63.6	0	0	Non-severe [PSI I–III >50%]	217	DXM 5 mg IV daily for 4 days	304
Wittermans 2021	NCT01743755	Netherlands	67.4	67.5	0	0	Non-severe [PSI I–III >50%]*	204.5	DXM 6 mg PO daily for 4 days	401
Snijders 2010	NCT00170196	Netherlands	58.2	63.5	10.3	NR	Non-severe [PSI I–III >50%]^	235.9	Prednisolone 40 mg daily for 7 days (IV or PO)	213
El-Ghamrawy 2006	NR	Saudi Arabia	61.8	61.8	100	NR	Severe [majority ICU patients]	NR	HCT 200 mg IV bolus, then 10 mg/h IV infusion for 7 days	34
McHardy and Schonell 1972	NR	Scotland	48.4	60.3	0	NR	Non-severe [defined by trials, most patients classified as mild–moderate]	NR	Prednisolone 5 mg every 6 h for 7 days	126
Fernández-Serrano 2011	ISRCTN22426306	Spain	66.7	61 (placebo), 66(MPDN)	0	0	Severe [fine scores IV–V >50%]	NR	MP 200 mg IV bolus, then 20 mg IV every 6 h for 3 days, then 20 mg IV every 12 h for 3 days, then 20 mg IV for 3 days	45
Torres 2015	NCT00908713	Spain	61.4	65.3	75	2.5	Severe [PSI scores IV–V >50%]	258.7	MP 0.5 mg/kg every 12 h for 5 days	120
Blum 2015 (STEP)	NCT00973154	Switzerland	62	74 (prednisone), 73 (placebo)	0	0	Non-severe [PSI I–III >50%]	161.5	Prednisone 5 mg PO daily for 7 days	785

Table 1 (continued)

Study	Trial registration	Country	Male (%)	Age	ICU (%)	Mechanical ventilation	Severity	CRP (mg/L)	Intervention	Number randomized
Marik 1993	NR	UK	NR	36.44	100	NR	Severe [mean Apache II score 13, all ICU patients]	NR	HCT 10 mg/kg IV once, 30 min prior to antibiotics	30
Wagner 1956	NR	USA	67.3	NR	NR	NR	Non-severe [as defined by authors]	NR	HCT PO taper over 5 day (starting with 200 mg/day, down to 2 mg/day)	113
Meduri 2022 (ESCAPe)	NCT01283009	USA	96	68.8	100	33	Severe [PSI scores IV–V >50%]	NR	MP 40 mg IV bolus, then 40 mg per day for 7 days, then taper for 20 days	584
Dequin 2023 (CAPE COD)	NCT02517489	France	69.4	67	100	22.2	Severe [PSI scores IV–V >50%]	250	HCT 200 mg IV daily for 4–8 days	795

* For mortality, we used in-study subgroups reported based on PSI scores (I–IV vs V)

^ For mortality, used in-study subgroups of PSI class IV/V vs I–III

& For mortality, we used in-study subgroups of vasopressor-only patients vs non-MV patients

HCT hydrocortisone, *MP* methylprednisolone, *DXM* dexamethasone

The median total dose used across trials was 70.3 mg (IQR 26.05 to 77.25) of dexamethasone equivalent, divided between 7 days for a daily dose equivalent of approximately 10 mg of dexamethasone equivalent/day.

Risk of Bias

For mortality, seven trials (43.7%, 1194 patients) were at probable or high risk of bias due to issues with the randomization process,[34–36,43,44,48,49] seven trials (43.7%) due to deviations from the intended interventions,[34–36,43,44,48,49] two trials were at risk of bias due to missing data (12.5%),[34,35] and four trials (25%) due to selective reporting of the results.[34,35,44,48] eTable 6 presents more details on the risk of bias assessments for all outcomes.

Mortality

Seventeen trials (4567 patients) reported on mortality, with 443 deaths.[34–38,40–50] For patients with more severe pneumonia, corticosteroids probably reduce mortality as compared to usual care (RR 0.62 [95% CI 0.45 to 0.85]; moderate certainty), with an absolute risk difference of 56 fewer deaths per 1000 patients [95% CI 81 to 22 fewer]. For patients with less severe pneumonia, corticosteroids may have no effect on mortality as compared to usual care (RR 1.08 [0.83 to 1.42]; low certainty), with an absolute risk difference of 6 more per 1000 (95% CI 13 fewer to 32 more). Figure 2 presents the forest plot and Table 2 presents the summary of findings.

We found a statistically significant (p=0.01) subgroup effect based on the severity of pneumonia and rated the credibility as moderate using the ICEMAN tool (eTable 7, eFigures 1-2). There was no subgroup effect based on the risk of bias, decade studied, or duration of corticosteroid use (eFigures 3-5). There was a statistically significant subgroup effect based on the type of corticosteroid in the subgroup analysis (p<0.001) and in meta-regression (p=0.001), with moderate/low credibility using ICEMAN. Figure 3 and eFigure 5-6 and eTable 7 present the results.

The TSA showed the required information size was not met (eFigure 7).

Dose Response

The dose-response meta-analysis demonstrated a non-linear dose-response relationship. We found that the highest impact on mortality was evident with relatively lower doses of dexamethasone or dexamethasone equivalents, with the optimal dosing being approximately 6 mg of dexamethasone daily for seven days (RR 0.45 [95% CI 0.0.32 to 0.68]). Relatively higher doses, above 11.5 mg of dexamethasone per day for 7 days, were associated with no effect or harm. Figure 4 and Table 3 present the dose-response curve data and eTable 8 presents goodness of fit statistics.

Invasive Mechanical Ventilation

Nine trials (2895 patients), with patients who did not require IMV at randomization, reported on the need for invasive mechanical ventilation, with 185 events.[34,36,38,42,45–48] Corticosteroids probably reduce the need for invasive mechanical ventilation as compared to usual care (RR 0.56 [95% CI 0.42 to 0.74]; moderate certainty), with an absolute risk difference of 82 fewer events per 1000 [95% CI 21 to 48 fewer].

There was no subgroup effect for non-severe versus severe, risk of bias, or type of corticosteroid or duration of treatment (eFigures 8-11), and Table 2 presents the summary of findings.

Need for ICU Admission

Five trials (2227 patients), with patients who did not require ICU at randomization reported on the need for ICU admission, with 95 events.[34,40,41,45,47] Corticosteroids probably reduce the need for ICU admission as compared to usual care (RR 0.65 [0.43 to 0.97]; moderate certainty) with an absolute risk difference of 18 fewer cases per 1000 [95% CI 2 to 29 fewer]. There was no subgroup difference for risk of bias, type of corticosteroid, or duration of treatment. eFigures 12-14 present the forest plots and Table 2 presents the summary of findings.

Duration of Hospitalization

Thirteen trials (3442 patients) reported on duration of hospitalization, with a mean duration of hospitalization of 12.8 days.[34–36,38–43,45–47,50] Corticosteroids may reduce the duration of hospitalization as compared to usual care (MD 2.31 days fewer [95% CI 0.76 to 3.85 fewer]; low certainty). There was no subgroup effect for severity, type of corticosteroid, or duration of treatment. There was a statistically significant subgroup effect for risk of bias; we took this into account when rating the certainty of the evidence (eTable 7). eFigures 15-18 present the forest plots and Table 2 presents the summary of findings.

Duration of ICU Stay

Eleven trials (926 patients) reported on duration of ICU stay, with a mean duration of hospitalization of 9.9 days.[36,38,40,43,45–48,50] Corticosteroids may reduce the duration of ICU stay (MD 2.1 days fewer [95% CI 0.50 to 3.61 days fewer]; low certainty). There was no subgroup effect for severity, risk of bias, type of corticosteroid, or duration of treatment (eFigures 19-23). Table 2 presents the summary of findings.

Adverse Events: Secondary Infections, Gastrointestinal Bleeding, and Hyperglycemia

Ten (2970 patients) trials reported on secondary infections,[35,38–40,42,43,46,47,50] eleven trials (3362) trials

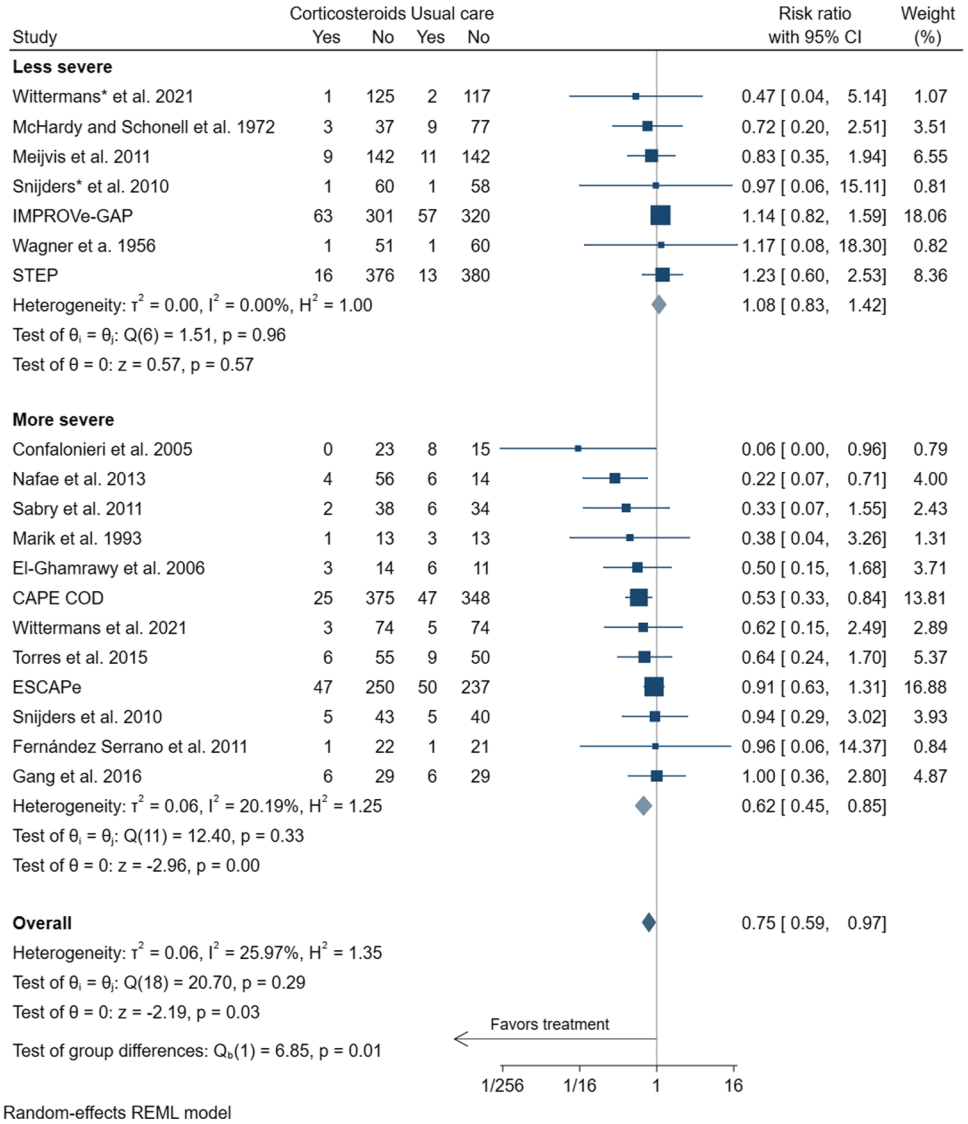

Figure 2 Forest plot for mortality based on severity subgroup. The left column shows the individual studies included in the meta-analysis, the middle column represents the effect sizes, and the right column shows the individual relative risks and their weight in contributing to the overall estimates.

reported on hyperglycemia,[34–36,39–42,45–47,50] and eleven trials (3368 patients) reported on gastrointestinal bleeding.[34–38,43,45–47,50] Corticosteroids may have no effect on the risk of secondary infections (RR 1.09 [95% CI 0.85 to 1.41]; low certainty) or gastrointestinal bleeding (RR 0.95 [95% CI 0.56 to 1.60]; low certainty) compared to usual care. Corticosteroids probably increase the risk of hyperglycemia when compared to usual care (RR 1.76 [95% CI 1.46 to 2.14]; moderate certainty) with an absolute risk difference of 58 more per 1000 (95% CI 35 more to 87 more).

Five trials reported on hyperglycemia requiring insulin,[34,35,42,45,50] whereas four reported only on the incidence of hyperglycemia.[36,39–41,46] However, there was no difference in the overall effect in the subgroup analysis (eFigure 36).

There was no subgroup effect for the type of corticosteroid, duration of treatment, or risk of bias for any of the adverse events. There was a statistically significant subgroup effect for severity and hyperglycemia, which we rated as low credibility. eFigures 24-36 present the forest plots and subgroups.

Table 2 Summary of Findings Table Presented in Both Relative Risk and Absolute Risk Differences with 95% Confidence Intervals

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE)	Relative risk (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with corticosteroids
Mortality (more severe)	2133 (12 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.62** (0.45 to 0.85)	146 per 1000	**56 fewer per 1000** (81 fewer to 22 fewer)
Mortality (less severe)	2434 (7 RCTs)	⨁⨁◯◯ Low[a,b]	**RR 1.08** (0.83 to 1.42)	75 per 1000	**6 more per 1000** (13 fewer to 32 more)
Invasive mechanical ventilation	2855 (9 RCTs)	⨁⨁⨁◯ Moderate[a]	**RR 0.56** (0.42 to 0.74)	82 per 1000	**36 fewer per 1000** (48 fewer to 21 fewer)
ICU admission	2277 (5 RCTs)	⨁⨁⨁◯ Moderate[b]	**RR 0.65** (0.43 to 0.97)	51 per 1000	**18 fewer per 1000** (29 fewer to 2 fewer)
Duration of hospitalization	3442 (13 RCTs)	⨁⨁◯◯ Low[f,g,h]	-	The mean duration of hospitalization was 12.8 days	MD **2.31 days fewer** (3.85 fewer to 0.76 fewer)
Duration of ICU stay	926 (9 RCTs)	⨁⨁◯◯ Low[g,h]	-	The mean duration of ICU stay was 9.9 days	MD **2.06 days fewer** (3.61 fewer to 0.46 fewer)
Ventilator-free days	630 (2 RCTs)	⨁⨁⨁◯ Moderate[b]	-	The mean ventilator-free days was 22 days	MD **2.9 days more** (0.95 more to 4.85 more)
Secondary infections	2970 (10 RCTs)	⨁⨁◯◯ Low[b,c]	**RR 1.09** (0.85 to 1.41)	77 per 1000	**7 more per 1000** (12 fewer to 32 more)
Hyperglycemia	3362 (11 RCTs)	⨁⨁⨁◯ Moderate[d]	**RR 1.76** (1.46 to 2.14)	76 per 1000	**58 more per 1000** (35 more to 87 more)
Gastrointestinal bleeding	3368 (11 RCTs)	⨁⨁◯◯ Low[e]	**RR 0.95** (0.56 to 1.60)	17 per 1000	**1 fewer per 1000** (8 fewer to 10 more)

[*]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

CI confidence interval, *MD* mean difference, *RR* risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Explanations

[a]Heterogenous definition of severity

[b]The confidence intervals include our MID/imprecision

[c]Heterogenous definition of infections

[d]Our outcome of interest was hyperglycemia requiring intervention, but most trials reported only hyperglycemia

[e]The confidence intervals cross our MID in both directions

[f]Statistically significant subgroup effect, with the most benefit from high risk of bias trials

[g]Critical heterogeneity

[h]Although there was no statistically significant difference in subgroups of risk of bias, most of the benefit is derived from three high risk of bias trials

Dose Response

The dose-response meta-analysis for hyperglycemia demonstrated both a non-linear and linear dose-response relationship, although the non-linear model is very uncertain for doses above 8.5 mg of dexamethasone/7 days. Both the non-linear and linear models suggest increasing harm with higher doses of corticosteroids.eTables 9 and 10 and eFigures 38-9 present the goodness of fit statistic and dose-response curve for hyperglycemia. eFigures 40-443 and eTables 11-14 present our publication bias assessments.

DISCUSSION

Main Findings

We present a comprehensive analysis examining the use of corticosteroids in hospitalized adult patients with CAP. We carefully evaluate between- and within-study subgroups to provide clinicians and evidence users with a nuanced assessment of specific patient populations that may benefit from corticosteroids. We found that corticosteroids reduce mortality in patients with severe CAP. We also demonstrate a non-linear dose-response relationship with mortality, with

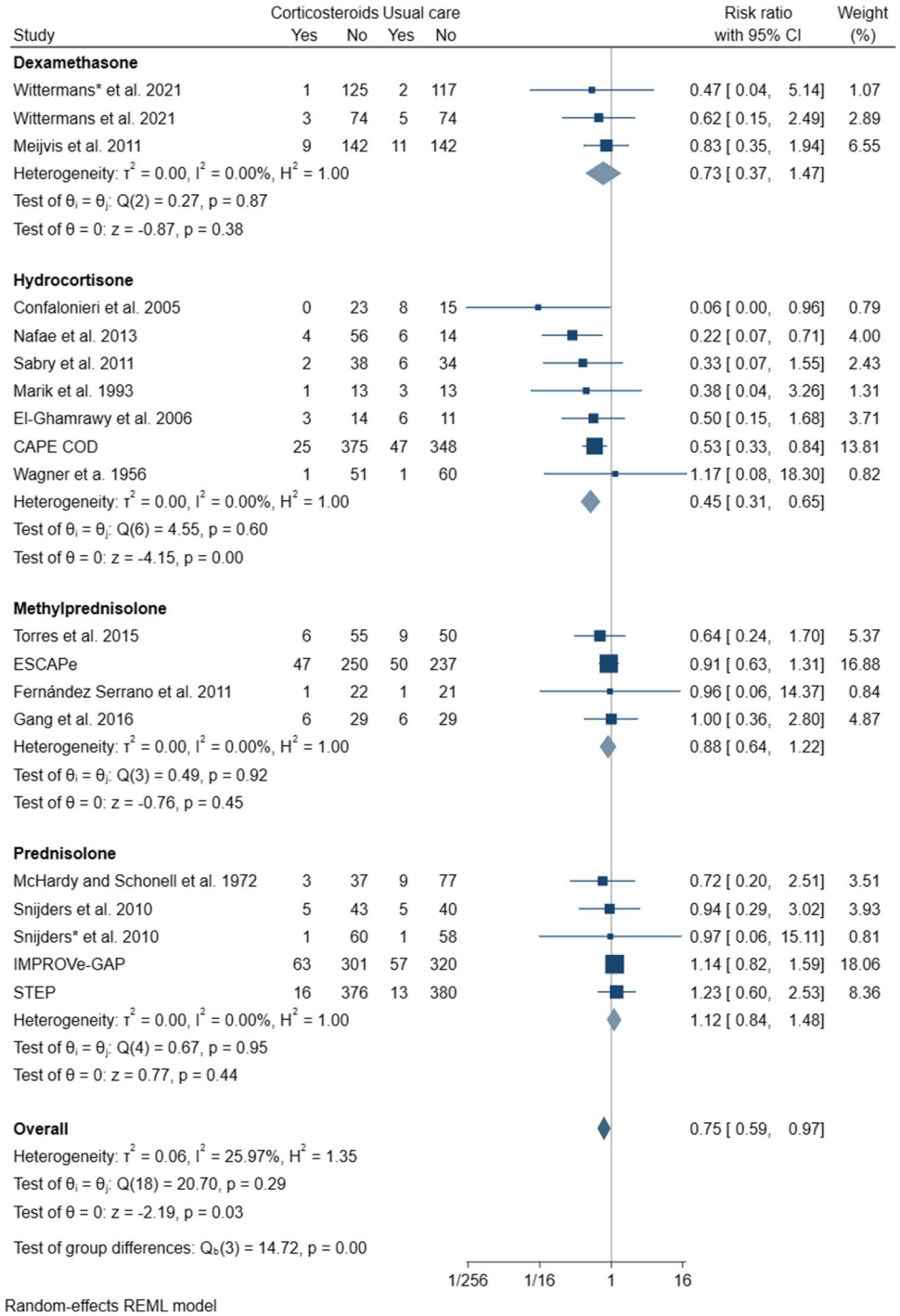

Figure 3 Forest plot for mortality based on corticosteroid type subgroup. The left column shows the individual studies included in the meta-analysis, the middle column represents the effect sizes, and the right column shows the individual relative risks and their weight in contributing to the overall estimates.

an optimal dose regimen that is relatively lower than the average used across trials. We found that corticosteroids probably reduce the risk of receiving invasive mechanical ventilation, and the need for ICU admission.

We also show that corticosteroids may reduce the duration of hospitalization and ICU stay, without substantially increasing the risk of secondary infections or GI bleeding. However, the use of corticosteroids may increase the incidence of hyperglycemia, requiring therapy such as insulin initiation or dose escalation.

In Relation to Other Findings

There have been two recent trials which showed diverging results. The recently published ESCAPe trial demonstrated no difference in 60-day mortality with corticosteroids

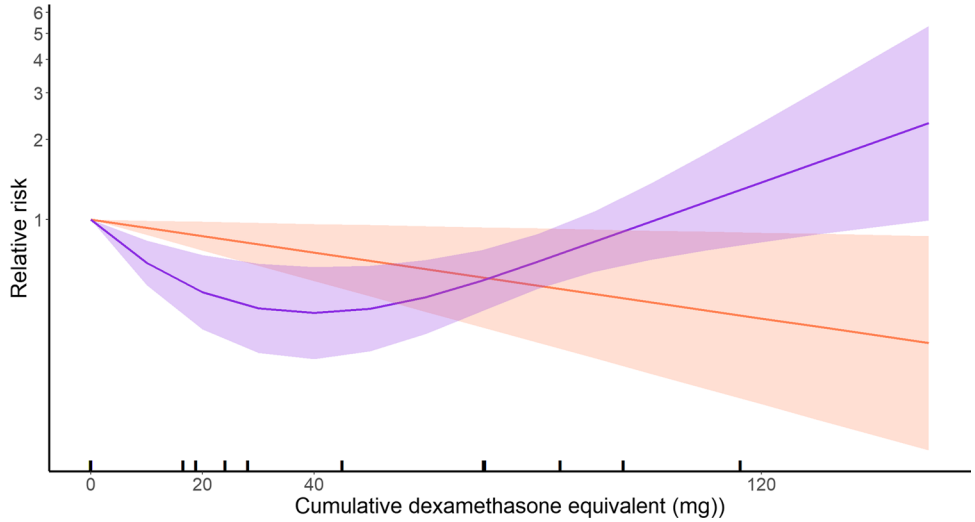

Figure 4 Dose-response curve. The curved purple line represents the non-linear dose-response relationship, and the purple ribbons represent 95% confidence intervals (95% CI). The yellow linear line represents the linear dose-response relationship, and the ribbons represent 95% CI.

(adjusted odds ratio 0.90, 95% CI 0.57 to 1.40).[50] The ESCAPe trial has other important considerations that may influence the internal and external validity of the findings including prolonged recruitment time, resulting in early trial termination.[38] In contrast, the recent CAPE COD trial demonstrated a favorable 28-day and 90-day mortality in patients with severe pneumonia receiving a median duration of hydrocortisone for 6 days (RR 0.53 [95% CI 0.33 to 0.84]). This study also has its limitations, namely it was stopped early for benefit.

Table 3 Non-linear Dose-Response Analysis, with Dose Represented as Dexamethasone (mg) Daily

Dexamethasone mg/day for 7 days	RR	95% CI lower	GRADE rating
1.5	0.69	0.57 to 0.84	⨁⨁◯◯ Low
3	0.53	0.39 to 0.74	⨁⨁◯◯ Low
4	0.46	0.32 to 0.68	⨁⨁◯◯ Low
6	0.45	0.3 to 0.66	⨁⨁⨁◯ Moderate
7	0.46	0.32 to 0.67	⨁⨁⨁◯ Moderate
8.5	0.51	0.37 to 0.7	⨁⨁⨁◯ Moderate
10	0.59	0.45 to 0.77	⨁⨁⨁◯ Moderate
11.5	0.7	0.55 to 0.88	⨁⨁◯◯ Low
13	0.83	0.64 to 1.07	⨁⨁◯◯ Low
14	0.98	0.71 to 1.36	⨁⨁◯◯ Low
16	1.16	0.77 to 1.76	⨁⨁◯◯ Low
17	1.38	0.82 to 2.31	⨁⨁◯◯ Low
18.5	1.64	0.88 to 3.05	⨁⨁◯◯ Low
20	1.94	0.94 to 4.04	⨁⨁⨁◯ Moderate
21	2.31	0.99 to 5.35	⨁⨁⨁◯ Moderate

The trials are similar in their trial design, sample size, and relatively similar corticosteroid dosing. One potentially important difference is the choice of corticosteroids. We found a moderate/low subgroup difference for hydrocortisone as compared to other corticosteroids. In fact, all the positive trials in this population, including the recent CAPE COD trial, have investigated hydrocortisone over alternatives.

Although previous systematic reviews and meta-analyses have demonstrated similar findings, we believe that this study provides important contributions. Specifically, as compared to the most recent review addressing this topic,[51] of which there are significant methodological limitations and the absence of the CAPE COD trial,[52] we have specifically evaluated for subgroup effect based on the severity of CAP and assess the credibility of potential subgroup effect using the ICEMAN tool. This subgroup analysis demonstrates that the effects of corticosteroids on mortality are limited to those with severe disease. Second, we have carefully applied GRADE which has led to substantial differences in certainty of evidence compared to the most recent review, leading to more nuanced conclusions regarding the effect of corticosteroid across outcomes. Third, to our knowledge, we are the first group to present a dose-response analysis informing the optimal dosing of corticosteroids in patients with severe CAP. We believe this is especially helpful given that previous guidelines often cite issues with uncertainty regarding optimal dose regimens. We converted the corticosteroid regimen to dexamethasone equivalents; however, previously there was currently no definitive evidence for use of one corticosteroid over another, although our analysis may provide some

evidence for hydrocortisone over alternatives. The corticosteroid type subgroup showed a statistical effect on the mortality primary outcome, but this finding was rated as moderate/low credibility, and there was no effect for any of the other outcomes. Fourth, we provide increased precision by including newly available RCTs such as the ESCAPe and CAPE COD trial which randomized a combined 1379 patients with severe CAP. Incorporating this new data, we are now able to demonstrate with improved certainty the benefit of corticosteroids for improving survival in patients with severe CAP.

The COVID-19 pandemic has increased the attention on this intervention given the efficacy of corticosteroids in patients with severe-to-critical COVID-19 pneumonia. The definitive trial demonstrating benefit in COVID-19 pneumonia came from a large platform trial (RECOVERY), which randomized over 6000 patients. In contrast, the totality of the evidence evaluating corticosteroids in CAP includes less than 5000 patients, highlighting the ongoing uncertainty of corticosteroids for this indication. Although COVID-19 and bacterial CAP are unique disease processes, the underlying pathophysiology driven by lung inflammation is likely similar and the consistent beneficial effect of corticosteroids in downregulating cytokine production and inhibition of neutrophil and macrophage migration to the lungs between conditions has good biological rationale. Furthermore, there is an established benefit for corticosteroids in ARDS, a disease state with increasing inflammatory dysregulation.

Strengths and Limitations

Strengths of our review include the addition of recent trials that provide important in-study subgroups evaluating the impact of disease severity, allowing for a better understanding of the appropriate population that is most likely to benefit from corticosteroids. Furthermore, the authorship group includes experts in CAP and meta-analysis. We also performed careful subgroup analysis and assessed the credibility of the analysis using the validated ICEMAN tool.

Limitations include the paucity of trials evaluating and reporting within-study subgroups. Most trials did not report in-study subgroups based on severity and severity was heterogeneously defined across the trials. Furthermore, we still have only low certainty evidence for several outcomes including adverse events as well as duration of ICU and hospitalization.

It is unclear whether the effect of corticosteroids is consistent across different causes of bacterial pneumonia (i.e., streptococcus pneumonia vs other causes). Future studies should examine microbiologic subgroups.

We included a small number of patients who had confirmed viral pneumonia. The effect of corticosteroids on viral pneumonia is unclear and our conclusions are limited to bacterial pneumonia. Future studies are needed to examine the effect of corticosteroids in patients with viral pneumonia.

We chose an optimal duration of corticosteroid administration based on the median duration included in randomized trials. There may be conditions such as secondary organizing pneumonia, or severe ARDS, which warrant longer durations than 7 days. Unfortunately, these patients were not included in these RCTs and therefore we are unable to analyze them. Furthermore, to minimize adverse events from corticosteroids, future studies should investigate optimal duration (e.g., 5 versus 7 days versus longer).

Implications and Future Directions

Clinical practice guidelines differ in their recommendations for the use of corticosteroids in severe CAP. The 2017 Society of Critical Care Medicine/European Society of Intensive Care Medicine Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency in Critically Ill Patients conditionally recommends the use of corticosteroids in patients hospitalized with CAP.[53] However, the American Thoracic Society (ATS), the Infectious Disease Society of America (IDSA), and the British Thoracic Society (BTS) recommended against the routine use of corticosteroids in CAP.[54] Concerns include a lack of clarity around which populations would benefit from corticosteroids, quality of the RCTs, safety, and consistency of existing meta-analyses. This review addresses some of these concerns and may provide further justification for using corticosteroids in this population, especially those with severe disease. Also, we offer clinicians guidance on optimal dosing for corticosteroids. These results should inform updates of clinical practice guidelines and may help decrease variation in practice recommendations. Further research is needed to better ascertain if certain types of patients with CAP are more likely to benefit from corticosteroids than others, based on specific severity criteria, biomarkers, or other considerations.

CONCLUSION

We show that corticosteroids reduce mortality in patients with severe pneumonia and probably reduce the need for invasive mechanical ventilation and the need for ICU admission. Corticosteroids probably increase the risk of hyperglycemia without an effect on the risk of secondary infections or GI bleeding.

Supplementary Information *The online version contains supplementary material available at https://doi.org/10.1007/s11606-023-08203-6.*

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Author Contribution: *T. P. and D. Z. conceived the study idea. T. P., D. A., and D. Z. screened trials, collected the data, performed the risk of bias assessments, and performed the GRADE assessments. T. P. performed all of the analysis. D. C., S. M. P., A. M. N., D. N., and B. R. provided expert analysis of the data and revised the GRADE assessments. B. R. provided key methodological input and supervision. All*

authors read and approved the final manuscript. B. R. and D. Z. supervised the study. T. P. is the data guarantor

Data Availability: *Data will be available on Open Science Framework upon publication.*

Declarations:

Conflict of Interest: *TP, DC, SMP, AMN, DN, and BR are members of the Society of Critical Care Medicine Corticosteroid Guidelines Focused Update Panel. SMP is the co-Chair of the Society of Critical Care Medicine Corticosteroid Guidelines Focused Update Panel. SMP discloses personal fees for advisory board work from AbbVie, royalty fees from McGraw Hill as textbook editor, and institutional grant support from the National Cancer Institute of the National Institutes of Health under Award Number P30CA008748, RevImmune, BioMerieux, and the Breast Cancer Research Foundation, outside the submitted work. No other authors made any disclosures.*

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