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# Impact of different corticosteroids on severe community-acquired pneumonia: a systematic review and meta-analysis

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## ABSTRACT

**Objectives** Randomised controlled trials (RCTs) have demonstrated conflicting results regarding the effects of corticosteroids on the treatment of severe community-acquired pneumonia (CAP). We aimed to investigate the efficacy and safety of different corticosteroids on patients who were hospitalised for severe CAP.

**Methods** We performed a systematic search through PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Scopus from inception to May 2023. The primary outcome was all-cause mortality. Data analysis was performed using a random-effects model.

**Results** A total of 10 RCTs comprising 1962 patients were included. Corticosteroids were associated with a lower rate of all-cause mortality (risk ratio (RR), 0.70 (95% CI 0.54 to 0.90); $I^2$=0.00%). When stratified into different corticosteroid types, hydrocortisone was associated with an approximately 50% lower mortality risk (RR, 0.48 (95% CI 0.32 to 0.72); $I^2$=0.00%). However, dexamethasone, methylprednisolone or prednisolone were not associated with an improvement in mortality. Furthermore, hydrocortisone was associated with a reduction in the rate of mechanical ventilation, acute respiratory distress syndrome, shock and duration of intensive care unit stay. These trends were not observed for dexamethasone, methylprednisolone or prednisolone. Corticosteroids were not associated with an increased risk of adverse events including gastrointestinal bleeding, secondary infection or hyperglycaemia.

**Conclusions** The use of hydrocortisone, but not other types of corticosteroids, was associated with a reduction in mortality and improvement in pneumonia outcomes among patients hospitalised with severe CAP.

PROSPERO registration number CRD42023431360.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Corticosteroids may provide mortality benefits in patients hospitalised for severe community-acquired pneumonia.

### WHAT THIS STUDY ADDS

⇒ Hydrocortisone, but not other corticosteroids, are associated with mortality benefits in patients hospitalised for severe community-acquired pneumonia.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Hydrocortisone may be used to treat patients hospitalised for severe community-acquired pneumonia.

## INTRODUCTION

Severe community-acquired pneumonia (CAP) is a life-threatening form of pneumonia with high morbidity and mortality.[1] In these patients, dysregulated lung and systemic inflammation can lead to sepsis, acute respiratory distress syndrome (ARDS) and end-organ damage.[2 3] Systemic corticosteroids downregulate proinflammatory cytokine production and have been hypothesised to mitigate systemic inflammation and organ dysfunction, leading to improved outcomes of severe pneumonia.[4 5]

Several randomised controlled trials (RCTs) have investigated the mortality benefits of adjunctive corticosteroids in patients with severe CAP, but the results have been inconclusive. For example, in the ESCAPe (Extended Steroid in Use in Community Acquired Pneumonia) and Santeon-CAP (dexamethasone in community-acquired pneumonia) trials, the use of methylprednisolone and dexamethasone did not improve mortality risk in patients with severe CAP.[6 7] However, the CAPE COD (community-acquired pneumonia: evaluation of corticosteroids) trial showed that hydrocortisone reduces all-cause mortality in patients with CAP admitted to an intensive care unit (ICU).[8]

Previous meta-analyses have attempted to address these inconsistencies by summarising evidence from RCTs,[9–11] but the data have been conflicting. In aggregate-data meta-analyses conducted by Siemieniuk and colleagues and Wu and colleagues,[10 11] corticosteroids were associated with a reduction in mortality in severe CAP. However, an individual patient

data meta-analysis performed by Briel and colleagues showed no mortality benefits associated with corticosteroids in severe CAP.[9] In a recent meta-analysis conducted by Pitre and colleagues, only hydrocortisone provided mortality benefits.[12] However, this analysis included both severe and non-severe CAP. Based on prior data, corticosteroids were associated with subgroup effects based on disease severity.[10] Therefore, an updated and focused meta-analysis is warranted to evaluate the effects of different corticosteroids on severe CAP. In this systematic review and meta-analysis, we aimed to evaluate the efficacy and safety of different types of corticosteroids in patients who were hospitalised for severe CAP.

## METHODS

### Data sources and searches

We conducted a systematic review through PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science and Scopus, searching for studies published from inception to May 2023, without language restrictions, using an approach that incorporated keywords including *pneumonia* and *corticosteroids* (online supplemental table 1). Referenced citations of included studies as well as articles citing the included studies were manually searched to identify any other potentially relevant studies. Articles published in languages other than English were interpreted using Google Translate. This study was performed in accordance with the PRISMA guidelines.[13] The review protocol is registered with PROSPERO (CRD42023431360).

### Study selection

Eligible studies were RCTs that investigated the effectiveness of intravenous or oral corticosteroid therapy in adults hospitalised for severe CAP. Corticosteroids included hydrocortisone, prednisolone, methylprednisolone and dexamethasone. Studies were required to report on at least one of the following outcomes: all-cause mortality, need for mechanical ventilation or development of serious complications of CAP or adverse events commonly associated with corticosteroids. Studies that focused on specific pneumonia populations, such as ventilator-associated pneumonia, aspiration pneumonia or Pneumocystis jirovecii pneumonia as well as those limited to specific patient populations such as chronic obstructive pulmonary disease or diabetes mellitus, were excluded from the analysis. Severe CAP was defined according to commonly used criteria: a Pneumonia Severity Index score of IV or V,[14] a CURB-65 (Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older) score greater than 2,[15] fulfilment of one major or three minor criteria from the 2007 consensus guideline of the Infectious Diseases Society of America and the American Thoracic Society,[16] a score of 3 or greater using British Thoracic Society criteria,[17] development of respiratory failure defined by a PaO2:FiO2 <300 or admission to the ICU (online supplemental table 2). Studies that enrolled patients with different severity of CAP were included if they reported subgroup data on severe CAP. The primary authors were contacted when subgroup data were not available in the published article.

The eligibility of each study was determined through a rigorous screening process conducted by two reviewers (CHa Chiang and CHu Chiang), who independently screened titles and abstracts, and obtained full texts of articles that were considered potentially eligible. The final inclusion of studies was determined through discussion with a third reviewer (JL). The inclusion and exclusion of included studies are summarised in online supplemental table 3.

### Data abstraction and quality assessment

Two reviewers (CHa Chiang and Y-CC) independently extracted data on study demographics and outcomes of interest. The outcomes were all-cause mortality, requirement for mechanical ventilation, duration of stay in the ICU and development of complications or adverse events including shock, ARDS, hyperglycaemia requiring treatment, secondary infection and gastrointestinal bleeding. Two reviewers (XYS and THW) evaluated the risk of bias in individual studies using the Cochrane risk-of-bias tool for randomised trials.[18] In cases of disagreements, a consensus was reached by discussing with a third reviewer (YPH).

### Data synthesis and analysis

We used a random-effects model based on the DerSimonian and Laird approach by using risk ratios (RRs) for dichotomous outcomes and mean differences for continuous outcomes. For outcomes with fewer than five studies, we used the Hartung-Knapp-Sidik-Jonkman model.[19 20] In studies reporting only the median, range and size of the trial, we approximated the means and SD using previously established techniques.[21] We used the inconsistency index ($I^2$) statistic to evaluate the extent of interstudy heterogeneity.[22] The $I^2$ value ranges from 0% to 100%, where $I^2<25\%$ signifies minimal heterogeneity, $25\%\leq I^2<50\%$ signifies moderate heterogeneity, $50\%\leq I^2<75\%$ signifies substantial heterogeneity and $I^2>75\%$ indicates large heterogeneity. Publication bias was evaluated through inspection of the Funnel's plot and statistical testing using the Egger's test.

For all outcomes, we compared the effects of different types of corticosteroids: dexamethasone, hydrocortisone, methylprednisolone and prednisolone on CAP outcomes. For the outcome of all-cause mortality, we performed additional subgroup analyses on potential sources of heterogeneity: risk of bias, cumulative dose of corticosteroids administered and geographic location of study. To calculate the cumulative dosages of corticosteroids, we converted all types of corticosteroids to the equivalent dosages of dexamethasone. We used the recommended dose of dexamethasone for the treatment of COVID-19 (ie, 6 mg/day for up to 10 days with a cumulative dose

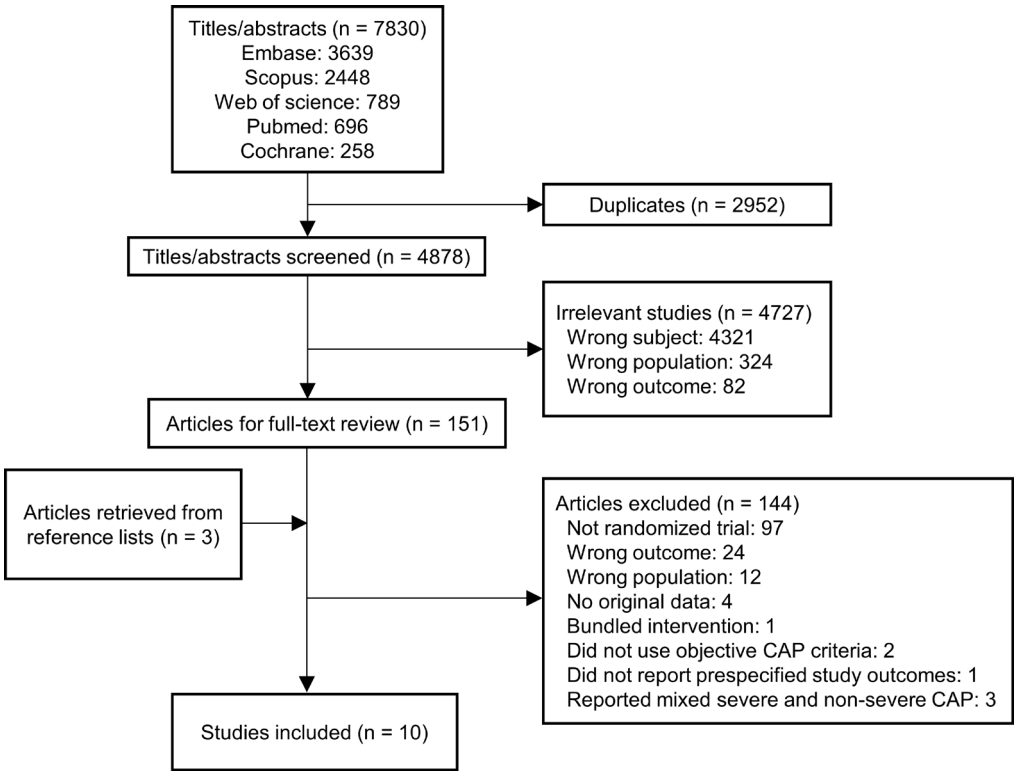


**Figure 1** Flowchart showing the process of systematic review. CAP, community-acquired pneumonia.

of 60 mg) as a cut-off to distinguish between low-dose and high-dose corticosteroids. To address differences between studies that could contribute to biased results, we performed sensitivity analyses by excluding studies that only included patients admitted to the ICU and studies that did not exclude patients with sepsis or septic shock. All analyses were performed using STATA V.16.0 (StataCorp, College Station, Texas). All p values were two-tailed and were considered statistically significant if less than 0.05.

## RESULTS

The initial search identified 7830 articles. After the removal of duplicates, 4878 articles remained. Of these articles, 151 studies underwent full-text review. Three trials were excluded because they included a mixed population of severe and non-severe CAP but did not report data on severe CAP.[23–25] One trial was excluded because it did not report on prespecified study outcomes.[26] We attempted to contact the authors of these trials through emails but did not obtain any responses. Two trials were excluded because they defined CAP severity based on clinical impression without the use of objective criteria.[27 28] One study used corticosteroids as part of a bundled intervention and was excluded.[29] Subsequently, a total of 10 studies were included in the final analysis (figure 1).

### Study characteristics

Among the 10 trials, 6 studies were conducted in Europe,[7 8 30–33] 2 in the USA[6 34] and 2 in the Middle East[35 36] (table 1). A total of 1962 patients were enrolled, with sample sizes ranging from approximately 30 to 800 hospitalised patients. Only one study received pharmaceutical funding.[7] The corticosteroid regimen varied across studies, including dexamethasone in one trial,[7] prednisolone in one trial,[31] methylprednisolone in three trials[6 32 33] and hydrocortisone in five trials.[8 30 34–36] All studies used a placebo in the control group. Most of the studies excluded patients who had conditions requiring corticosteroids prior to enrolment.[6–8 30–33 35] Two trials excluded patients with sepsis or septic shock[8 32] (online supplemental table 4).

### Risk-of-bias assessment

Among the 10 studies included, 9 trials were double blinded[6–8 30–33 35 36] and 1 trial was open labelled[34] (table 1). Six studies were evaluated as having a low risk of bias,[6–8 30 31 33] while four studies were determined to have some concerns over the risk of bias due to the randomisation process.[32 34–36] Two studies also had some risk of bias in the measurement of the outcome[34 35] (online supplemental table 5).

### Outcomes

#### All-cause mortality

All studies (1962 patients) reported on outcomes in all-cause mortality. Corticosteroids were associated with

**Table 1** Summary of study characteristics

| Trial (author, year) | Country | Study design | Industry funding | Severity score used for defining severe CAP | Number of patients | | | Type of corticosteroid | Corticosteroid dosing strategy | Timing of treatment initiation | Equivalent cumulative dose of dexamethasone * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Total | Control | Corticosteroid | | | | |
| Marik *et al*[34] 1993 | United States | Open-label | Not reported | BTS and ICU admission | 30 | 16 | 14 | Hydrocortisone | Hydrocortisone 10 mg/kg IV 30 min before antibiotics | 30 mins prior to starting antibiotic therapy | 28 mg |
| Confalonieri *et al*[30] 2005 | Italy | Double-blinded, placebo-controlled | Not reported | ATS 1993, and ICU or RICU admission | 46 | 23 | 23 | Hydrocortisone | Hydrocortisone 200 mg IV bolus followed by 10 mg/h IV for 7 days | Not reported | 75 mg |
| El Ghamrawy *et al*[35] 2006 | Saudi Arabia | Double-blinded, placebo-controlled | Not reported | ATS 2001 | 34 | 17 | 17 | Hydrocortisone | Hydrocortisone 200 mg IV bolus followed by 10 mg/h for 7 days | Not reported | 75 mg |
| Snijders *et al*[31] 2010 | The Netherlands | Double-blinded, placebo-controlled | No | CURB-65>2 or PSI class IV-V | 93 | 45 | 48 | Prednisolone | Prednisolone 40 mg IV or orally for 7 days | Not reported | 42 mg |
| Sabry *et al*[36] 2011 | Egypt | Double-blinded, placebo-controlled | No | ATS 2007 | 80 | 40 | 40 | Hydrocortisone | Hydrocortisone 200 mg IV bolus, followed by hydrocortisone 12.5 mg/h IV for 7 days | Not reported | 92 mg |
| Fernández-Serrano *et al*[32] 2011 | Spain | Double-blinded, placebo-controlled | No | Respiratory failure ($PaO_2/FiO_2$<300) | 45 | 22 | 23 | Methylprednisolone | Methylprednisolone 200 mg IV bolus, followed by tapering infusion (20 mg/6 hour for 3 days, 20 mg/12 hours for 3 days, and 20 mg/day for 3 days) over 9 days | 30 min before starting the antibiotic treatment | 117 mg |
| Torres *et al*[33] 2015 | Spain | Double-blinded, placebo-controlled | No | Modified ATS criteria or PSI V | 120 | 59 | 61 | Methylprednisolone | Methylprednisolone 0.5 mg/kg IV twice daily for 5 days | Within 36 hours of hospital admission | 70 mg |
| Wittermans *et al*[7] 2021 | The Netherlands | Double-blinded, placebo-controlled | Yes | PSI IV-V | 156 | 79 | 77 | Dexamethasone | Dexamethasone 6 mg oral daily for 4 days | Within 24 hours of emergency department presentation | 24 mg |
| Meduri *et al*[6] 2022 | United States | Double-blinded, placebo-controlled | No | Modified ATS/IDSA criteria, and ICU or intermediate admission | 563 | 277 | 286 | Methylprednisolone | Methylprednisolone 40 mg bolus followed by methylprednisolone 40 mg daily on days 1–7, 20 mg daily on days 8–14, 12 mg daily on days 15–17 and 4 mg daily on days 18–20. | On the day of randomisation | 96 mg |

Continued

**Table 1** Continued

| Trial (author, year) | Country | Study design | Industry funding | Severity score used for defining severe CAP | Number of patients | | | Type of corticosteroid | Corticosteroid dosing strategy | Timing of treatment initiation | Equivalent cumulative dose of dexamethasone * |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Total | Control | Corticosteroid | | | | |
| Dequin *et al*[8] 2023 | France | Double-blinded, placebo-controlled | No | Initiation of MV, initiation of high-flow nasal canula, $PaO_2$:$FiO_2$ ratio<300, or PSI V | 795 | 395 | 400 | Hydrocortisone | Hydrocortisone 200 mg IV daily for 4 days. A total of 8 or 14 days of hydrocortisone course determined by predefined clinical criteria. 200 mg IV hydrocortisone daily on day 1–7, 100 mg daily on day 8–11 and 50 mg daily on day 12–14 in 14 days treatment. 200 mg IV hydrocortisone daily on day 1–4, 100 mg daily on day 5–6 and 50 mg daily on day 7–8 in 8 days treatment. | Within 24 hours of onset of any severity criterion: requirement of mechanical ventilation, high flow nasal cannula with $PaO_2$:$FiO_2$<300 and FiO2>50%, or nonbreathing mask with $PaO_2$:$FiO_2$<300 and FiO2>50%, PSI index score>130 | 44 mg or 78 mg |

*Corticosteroid converted to dexamethasone equivalent dose for 70 kg adult. Note that the conversion factors were as follows: dexamethasone:hydrocortisone 1:25; dexamethasone: prednisolone 1:6.7; dexamethasone:methylprednisolone 1:5.3. Equivalent cumulative dose of dexamethasone was rounded off to the nearest whole number.
ATS, American Thoracic Society; BTS, British Thoracic Society; CORB, Confusion, Oxygenation, Respiratory rate, Blood pressure; CURB-65, Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, and age 65 or older; $FiO_2$, fraction of inspired oxygen; ICU, intensive care unit; IDSA, Infectious Disease Society of America; IV, intravenous; MV, mechanical ventilation; $PaO_2$, arterial blood oxygen pressure; PEEP, positive end expiratory pressure; PSI, Pneumonia Severity Index; RICU, respiratory intensive care unit.

a 30% lower rate of all-cause mortality compared with placebo (RR, 0.70 (95% CI 0.54 to 0.90); $I^2$=0.00%) (figure 2). The mortality benefits varied according to the type of corticosteroid used. Patients receiving hydrocortisone had an approximately 50% lower mortality risk as compared with placebo (RR, 0.48 (95% CI 0.32 to 0.72); $I^2$=0.00%). On the other hand, patients receiving dexamethasone, methylprednisolone or prednisolone did not experience a reduction in mortality. There is no publication detected on the funnel plot (online supplemental figure 1).

### Mechanical ventilation

Six studies (763 patients) reported on outcomes in mechanical ventilation. Corticosteroids were associated with about 50% lower rate of mechanical ventilation compared with placebo (RR, 0.54 (95% CI 0.43 to 0.67); $I^2$=0.00%) (online supplemental figure 2). Patients who received hydrocortisone experienced an approximately 50% reduction in the need for mechanical ventilation (RR, 0.54 (95% CI 0.43 to 0.69); $I^2$=0.00%), whereas patients who received methylprednisolone did not experience this reduction (RR, 0.44 (95% CI 0.17 to 1.10); $I^2$=0.00%).

### Acute respiratory distress syndrome

Four studies (666 patients) reported on the outcome of ARDS. Corticosteroids were associated with a 55% lower rate of ARDS compared with placebo, but this risk reduction was not statistically significant (RR, 0.45 (95% CI 0.14 to 1.43); $I^2$=40.49%) (online supplemental figure 3). Patients who received hydrocortisone experienced a 77% reduction in ARDS (RR, 0.23 (95% CI 0.07 to 0.82); $I^2$=3.46%), whereas patients who received methylprednisolone did not experience this reduction (RR, 1.14 (95% CI 0.46 to 2.83)).

### Shock

Seven studies (1573 patients) reported on the outcome of shock. Corticosteroids were associated with a 60% lower rate of shock compared with placebo (RR, 0.40 (95% CI 0.21 to 0.77); $I^2$=53.03%) (online supplemental figure 4). Patients who received hydrocortisone experienced a 78% reduction in shock (RR, 0.22 (95% CI 0.06 to 0.74); $I^2$=67.29%), whereas patients who received methylprednisolone did not experience this reduction (RR, 0.69 (95% CI 0.29 to 1.63); $I^2$=22.93%).

### Duration of ICU stay

Five studies (1808 patients) reported on the duration of ICU stay. Corticosteroids were associated with a shorter duration of ICU stay compared with placebo (mean difference, −0.92 (95% CI −1.68 to −0.17) days; $I^2$=43.36%) (online supplemental figure 5). Hydrocortisone, but not methylprednisolone, was associated with a shorter duration of ICU stay (mean difference, −1.27 (95% CI −1.91 to −0.64) days; $I^2$=0.00%).

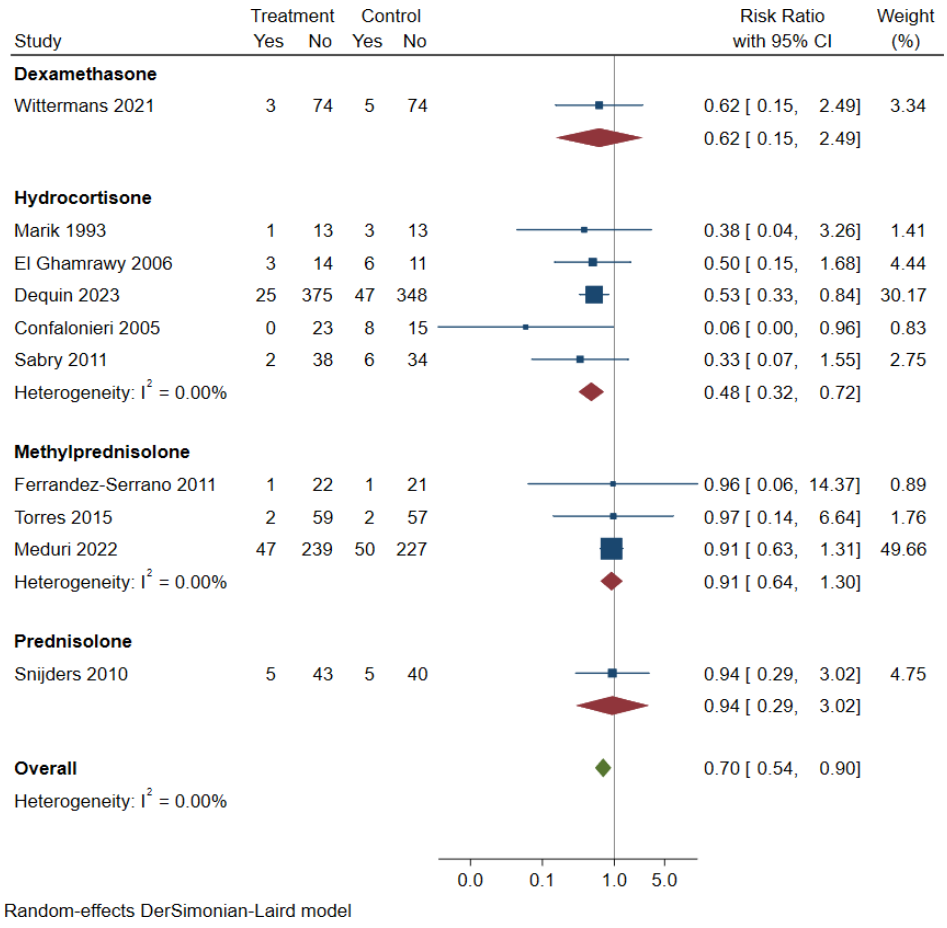


**Figure 2** Forest plot summarising the effects of corticosteroids on all-cause mortality. Note: The inconsistency index ($I^2$) statistic indicates the extent of inter-study heterogeneity.

### Adverse events

The use of corticosteroids was not associated with an increased risk of gastrointestinal bleeding or secondary infection regardless of the type of corticosteroids. There appeared to be a trend towards a higher risk of hyperglycaemia in patients treated with methylprednisolone compared with placebo, though this was not statistically significant (RR, 1.40 (0.93 to 2.11); $I^2$=4.98%). The results are summarised in online supplemental figures 6–8.

### Sensitivity analyses

In studies that did not use ICU admission as an inclusion criterion, corticosteroids appeared to be associated with a lower risk of all-cause mortality, though this effect was not statistically significant (RR, 0.64 (0.35 to 1.16); $I^2$=0.00%). Similarly, hydrocortisone appeared to be associated with a lower risk of all-cause mortality, though this effect was not statistically significant (RR, 0.43 (0.17 to 1.11); $I^2$=0.00%). In studies that excluded patients with sepsis or septic shock, hydrocortisone was associated with a lower risk of all-cause mortality (RR, 0.53 (0.33 to 0.84); $I^2$=0.00%). These results are summarised in online supplemental figures 9 and 10.

### Subgroup analyses

There was no statistical difference in the risk of mortality between studies that had low versus high risk of bias, used cumulative high-dose versus low-dose corticosteroids, performed in Europe versus outside of Europe and duration of corticosteroids less than versus more than 7 days (online supplemental figures 11–14).

## DISCUSSION

In this updated meta-analysis of 10 studies comprising 1962 patients, the use of corticosteroids results in a reduction in overall mortality in patients with severe CAP. In particular, hydrocortisone reduces the risk of all-cause mortality. These clinical benefits were not observed for other types of corticosteroids.

Prior to this study, three meta-analyses have examined the use of corticosteroids in patients with severe CAP, but the results have been inconclusive.[9–11] In 2015, in an aggregated-data meta-analysis of six trials, Siemieniuk and colleagues found that adjunctive corticosteroids reduced mortality in severe CAP by about 60% (RR 0.39 (95% CI 0.20 to 0.77)). The authors also reported that corticosteroids were associated with a reduction in mechanical ventilation and ARDS.[10] In 2018, in an individual patient

data meta-analysis of five trials, Briel and colleagues found that adjunctive corticosteroids did not provide significant mortality benefits for patients with severe CAP (RR 0.70 (95% CI 0.44 to 1.13)).[9] Nevertheless, subsequently in 2023, in an aggregated-data meta-analysis of seven trials,[11] Wu and colleagues reported that corticosteroids were associated with an approximately 40% reduction in 30-day mortality among patients hospitalised with severe CAP (RR 0.61 (95% CI 0.44 to 0.85)). One recent meta-analysis performed by Pitre and colleagues did report hydrocortisone to be associated with mortality benefits.[12] However, these results were likely confounded by disease severity as the analysis included both severe and non-severe CAP. Prior data have demonstrated that corticosteroids can have subgroup effects depending on disease severity.[10] In this updated meta-analysis of 10 trials, we found that corticosteroids were associated with a reduction in mortality among patients with severe CAP. The novel finding of this study was that hydrocortisone, but not other types of corticosteroids, was associated with an approximately 50% reduction in mortality among patients with severe CAP. Furthermore, hydrocortisone, but not other corticosteroids, was associated with concomitant benefits in secondary outcomes such as reductions in mechanical ventilation, ARDS, shock and duration of stay in the ICU. This result was critical because it suggests that there are differential effects of corticosteroids on severe CAP and only hydrocortisone was associated with improved outcomes among patients hospitalised for severe CAP.

Overall, the clinical benefits associated with corticosteroids in patients with severe CAP appeared to be driven by the positive effects of hydrocortisone. Whether this finding represents a class effect in that only hydrocortisone provides outcome benefits in severe CAP or a difference between studies was not entirely clear. In most of the included studies, hydrocortisone was dosed at 200 mg/day, which was similar in terms of equivalent dosing in other corticosteroid groups. In our subgroup analyses, mortality outcomes did not differ based on the doses of corticosteroids given to patients. Therefore, the differences in mortality benefits between different corticosteroids were unlikely to be related to dose differences. We explored the effects of geography and risk of bias on all-cause mortality and did not find a difference in outcomes between studies performed in different geographical regions and studies with a low versus high risk of bias. We also performed a sensitivity analysis by excluding studies that focused on ICU patients as the clinical effects of corticosteroids were thought to have greater benefits in patients admitted immediately to the ICU than those admitted to the regular wards. In this sensitivity analysis, corticosteroids, and primarily hydrocortisone, showed a trend towards a reduction in all-cause mortality among patients admitted to the regular wards, similar to the primary analysis. Therefore, the mortality benefits of hydrocortisone on severe CAP may be generalised to the non-ICU population. Given these findings, patients who were not admitted to the ICU but fulfilling severe CAP criteria may be considered for hydrocortisone treatment.

Hydrocortisone is a short-acting glucocorticoid with low potency. By contrast, prednisolone, methylprednisolone and dexamethasone are longer acting glucocorticoids with higher potency than hydrocortisone.[37] Mechanistically, hydrocortisone may modulate the immune response and reduce inflammation without excessive immune activation, whereas other corticosteroids may lead to prolonged immunosuppression, potentially hindering the host response against infection. Thus, hydrocortisone's shorter duration of action and lower potency may allow for anti-inflammatory effects without significant immunosuppression, contributing to its observed mortality benefits in severe CAP. Furthermore, hydrocortisone acts as a glucocorticoid with both glucocorticoid and mineralocorticoid effects, whereas dexamethasone and methylprednisone, being synthetic glucocorticoids, predominantly exert glucocorticoid effects with minimal mineralocorticoid activity.[38] Mineralcorticoid plays a pivotal role in regulating sodium and potassium balance.[39] This dual effect of hydrocortisone, encompassing both glucocorticoid and mineralocorticoid actions, may confer unique therapeutic advantages, particularly in the context of severe CAP, where maintaining fluid balance and blood pressure is crucial during heightened stress conditions.

Previous meta-analyses focusing on sepsis showed that hydrocortisone, but not other corticosteroids, was associated with sepsis reversal and mortality benefits.[40 41] Of the 10 studies included in this meta-analysis, 2 studies excluded patients with sepsis or septic shock. In the pooled analysis of studies that excluded sepsis or septic shock, hydrocortisone remained to be associated with a reduction in CAP mortality. Thus, hydrocortisone likely potentiates mortality benefits in severe CAP via mechanisms other than shock reversal. For example, hydrocortisone has been shown to improve the PaO2/FiO2 and lung injury score in patients with sepsis-associated ARDS.[42] Similarly, Sabry and Omar reported that hydrocortisone improved PaO2/FiO2 in patients with CAP.[36] Consistent with these observations, we found that hydrocortisone was associated with reductions in the need for mechanical ventilation and the occurrence of ARDS. There were three studies comprising approximately 750 patients that investigated the effects of methylprednisolone in severe CAP.[6 32 33] In our pooled analyses, methylprednisolone was not associated with mortality benefits or improvements in pneumonia-related outcomes, suggesting that methylprednisolone likely does not improve overall outcomes in patients with severe CAP. Nevertheless, there was only one study each that investigated the effects of dexamethasone or prednisolone in severe CAP, and, therefore, it remained unclear if these two types of corticosteroids might provide clinical benefits for patients with severe CAP. Interestingly, dexamethasone has been demonstrated to reduce mortality in patients with ARDS and COVID-19, though the mortality benefits were not

superior to methylprednisolone.[43–45] It is unclear why there was a discrepancy between our study and prior COVID studies. Potential explanations include differences in response to corticosteroids between COVID pneumonia and CAP, and only a single study (and inadequate statistical power) investigating the effects of dexamethasone in CAP.

The current study is subjected to several limitations. First, there were differences in inclusion and exclusion criteria, the definition of severe CAP as well as administration routes and dosages of corticosteroids among the included studies, which might contribute to some degree of interstudy heterogeneity. For example, in the study conducted by Marik and colleagues, a single dose of hydrocortisone was used; in other studies, a prolonged duration of corticosteroids was used. The initiation time of corticosteroids also varied among studies. In the study performed by Dequin and colleagues, hydrocortisone was administered within 24 hours of enrolment; however, in the trial performed by Meduri and colleagues, methylprednisolone was administered up to 96 hours of enrolment.[46] Furthermore, the initiation time of corticosteroids was unreported in many studies. Because we did not have access to individual patient data, we were unable to assess how these differences might influence the reported outcomes. Nevertheless, we were able to minimise potential interstudy heterogeneity by stratifying corticosteroids into their subtypes; accordingly, the measure of interstudy heterogeneity, $I^2$, was non-substantial across most reported outcomes. We also performed multiple subgroup analyses to identify potential sources of heterogeneity, such as different corticosteroid dosages, geographical regions and risk of bias. Second, the generalisability of our findings may be limited due to the exclusion of certain patient populations in most primary studies. For example, most studies excluded patients who were immunosuppressed, pregnant, with recent gastrointestinal bleeding or at high risk for neuropsychiatric adverse effects. It is unclear how the results of this study apply to these populations. Third, the number of studies and sample size in some of the reported outcomes were small and likely underpowered for some types of corticosteroids after stratification. Fourth, the data presented in this study were limited to hospitalised patients with severe CAP and do not apply to patients with less severe CAP. Therefore, the effects of corticosteroids on less severe CAP remain unclear. Fifth, we used mean differences for continuous outcomes, even though reductions in the duration of ICU or hospital stay were probably not normally distributed. Finally, we were not able to evaluate for publication bias through the funnel plot for most of the outcomes due to the small number of studies available.

In conclusion, the use of hydrocortisone was associated with a reduction in overall mortality and improvement in pneumonia-related outcomes among patients with severe CAP. Other types of corticosteroids did not appear to provide these benefits though these analyses were limited by the number of studies available. Further RCTs are needed to evaluate the effects of dexamethasone and prednisolone on severe CAP.

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