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ORIGINAL ARTICLE

# Patient-Level Meta-Analysis of Low-Dose Hydrocortisone in Adults with Septic Shock

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## Abstract

**BACKGROUND** Trials and study-level meta-analyses have failed to resolve the role of corticosteroids in the management of patients with septic shock. Patient-level meta-analyses may provide more precise estimates of treatment effects, particularly subgroup effects.

**METHODS** We pooled individual patient data from septic shock trials investigating the adjunctive use of intravenous hydrocortisone. The primary outcome was 90-day all-cause mortality, and it was also analyzed across predefined subgroups. Secondary outcomes included mortality at intensive care unit and hospital discharge, at 28 and 180 days, and vasopressor-, ventilator-, and organ failure–free days. Adverse events included superinfection, muscle weakness, hyperglycemia, hypernatremia, and gastroduodenal bleeding.

**RESULTS** Of 24 eligible trials (n=8528), 17 (n=7882) provided individual patient data, and 7 (n=5929) provided 90-day mortality. The marginal relative risk (RR) for 90-day mortality of hydrocortisone versus placebo was 0.93 (95% confidence interval [CI], 0.82 to 1.04; P=0.22; moderate certainty). It was 0.86 (9% CI, 0.79 to 0.92) for hydrocortisone with fludrocortisone and 0.96 (95% CI, 0.82 to 1.12) without fludrocortisone. There was no significant differential treatment effect across subgroups. Hydrocortisone was associated with little to no difference in any of the secondary outcomes except vasopressor-free days (mean difference, 1.24 days; 95% CI, 0.74 to 1.73; high certainty). Hydrocortisone may not be associated with an increase in the risk of superinfection (RR, 1.04; 95% CI, 0.95 to 1.15; low certainty), hyperglycemia (RR, 1.05; 95% CI, 0.98 to 1.12; low certainty), or gastroduodenal bleeding (RR, 1.11; 95% CI, 0.83 to 1.48; low certainty). Hydrocortisone may be associated with an increase in the risk of hypernatremia (RR, 2.01; 95% CI, 1.56 to 2.60; low certainty) and muscle weakness (n=2647; RR, 1.73; 95% CI, 1.49 to 1.99; low certainty).

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**CONCLUSIONS** In this patient-level meta-analysis, hydrocortisone compared with placebo was not associated with reduced mortality for patients with septic shock. (Funded by "Programme d'Investissements d'Avenir," a research Professorship from the National Institute of Health and Care Research, Leadership Fellowships from the National Health and Medical Research Council of Australia, and Emerging Leaders Fellowship from the National Health and Medical Research Council of Australia; PROSPERO registration number, CRD42017062198.)

# Introduction

Sepsis is a global health priority affecting 55 million patients worldwide and causing 11 million deaths annually.[1] Treatment for sepsis may include prompt recognition, source control, antibiotics, fluids, vasopressors, and adjunctive therapies.[2] Corticosteroids have been evaluated as adjunctive therapy for septic shock for more than 50 years. Despite this substantive body of research, uncertainty persists about the effects of corticosteroids on mortality.[3] Two recent, adequately powered randomized controlled trials in adults with septic shock (APROCCHSS [Activated Protein C and Corticosteroids for Septic Shock[4]] and ADRENAL [Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock[5]]) investigated the effects of an intravenous dose of 200 mg hydrocortisone for 7 days and reported conflicting effects on mortality; they both reported earlier shock reversal and earlier liberation from mechanical ventilation with glucocorticoids, however. Several trial-level meta-analyses[6,7] since the publication of APROCCHSS and ADRENAL have reported divergent results of glucocorticoids on mortality, although beneficial effects were reported with respect to intensive care unit (ICU) length of stay, duration of shock, and duration of mechanical ventilation.

Sepsis is defined by using a syndromic approach that does not consider the pathobiology, patient heterogeneity, or complexity of the host response.[8] Consequently, treatment effects of glucocorticoids in patient subgroups or particular settings could have been missed that may be identified only by patient-level meta-analyses. Patient-level meta-analysis has advantages compared with trial-level meta-analysis,[9] in particular, the ability to define consistent inclusion and exclusion criteria to assess subgroups defined consistently across studies and to conduct time-to-event analysis. We undertook a patient-level meta-analysis to assess the effect of hydrocortisone versus usual care on 90-day mortality, secondary clinical outcomes, and adverse effects and to compare the effects of hydrocortisone across prespecified patient subgroups.

# Methods

## PROTOCOL AND REGISTRATION

This study was undertaken according to *The Cochrane Handbook for Systematic Reviews of Interventions*[10] using a prepublished protocol[11] and registered prospectively on PROSPERO (CRD42017062198). This report complies with current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of individual participant data.[12] The PRISMA checklist was followed. This study used existing data from completed randomized clinical trials and complied with the ethical and regulatory requirements regarding data sharing for each of the component trials.

## ELIGIBILITY CRITERIA

Randomized controlled trials were included that were approved by a human research ethics committee, included adults with sepsis or septic shock in which the intervention was intravenous hydrocortisone at a maximal daily dose of 400 mg for at least 72 hours, the comparison groups received placebo or usual care or alternate dosing regimens of hydrocortisone, and the trial reported at least one of the prespecified outcomes for this review.

## SEARCH STRATEGY AND STUDY SELECTION

The search strategy is detailed in Section 1.6 of the Supplementary Appendix and was published before completion.[11] In brief, we searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2020 Issue 9) MEDLINE ALL (Ovid SP), Embase (Ovid SP), and Latin American Caribbean Health Sciences Literature (LILACS) using the search terms "sepsis," "septic shock," "steroids," and "corticosteroids." The electronic search was completed in September 2020. The search of the gray literature (i.e., material published in nontraditional academic or commercial publications) included checking the reference lists of all trials identified by these methods and the proceedings of annual meetings of major critical care medicine societies.

Screening of articles was done using Excel, and de-duplication of studies was done manually. No language or publication status restrictions were applied. Study screening was performed by two blinded reviewers with disagreements resolved by consensus and third-party adjudication when consensus could not be reached.

### DATA COLLECTION PROCESSES AND DATA INTEGRITY

Individual patient-level data were requested from all studies identified by the search. Two reviewers (R.P. and D.A.) independently checked data supplied for included trials for missing data, internal data consistency, randomization integrity, and follow-up and censoring patterns. Any discrepancies or unusual patterns were resolved with the original study's corresponding author. For studies that did not provide individual patient data, trial-level data were extracted independently by two authors, with disputes resolved by discussion.

### DATA ITEMS

The final data set specification is provided in the data harmonization table (Supplementary Appendix, Section 1.7). In brief, we requested data regarding the intervention, including dose, mode of delivery (bolus or infusion), mode of discontinuation of therapy (tapered or abrupt), duration (fixed or variable according to vasopressor treatment), and inclusion of enterally administered fludrocortisone. Details regarding the comparison group (placebo or usual care or details of an active intervention), data regarding baseline characteristics of the included trial participants (age, sex, vasopressor dependency, vasopressin use, indices of severity of illness, arterial lactate concentration, and exposure to etomidate), and data required to assess the specified patient-level subgroups and outcomes were also collected.

### PRESPECIFIED SUBGROUPS

The primary analysis was conducted in trial participants with septic shock, defined by systolic blood pressure less than 100 mm Hg or mean arterial pressure less than 65 mm Hg after fluid resuscitation, arterial lactate levels greater than 2.0 mmol/l, or treatment with vasopressors to maintain adequate blood pressure. We predefined patient-level subgroups[10] based on age, sex, preexisting conditions associated with an altered hypothalamic-pituitary or renin-angiotensin-aldosterone axis, baseline-predicted mortality from Simplified Acute Physiology Score II (range, 0 to 163 [with higher scores indicating greater severity of illness])[12] or Acute Physiology and Chronic Health Evaluation II (scale from 0 to 71 [with higher scores indicating a higher risk of death[13]]) scores, Sequential Organ Failure Assessment (SOFA; scale of 0 to 4 for each of six organ systems [with higher scores indicating more severe organ dysfunction])[14] score and its components, criteria for Sepsis-3 (Third International Consensus Definitions for Sepsis and Septic Shock),[8] infection characteristics (community acquired vs. hospital acquired, medical vs. surgical, lung vs. other sources of infection, and gram-negative vs. gram-positive vs. polymicrobial), arterial lactate concentration, response to the standard corticotropin test (increase in peak cortisol levels by >250 vs. <250 nmol/l from baseline value), vasopressor dependency, vasopressin, etomidate, appropriate antibiotic as reported in trials, and timing of hydrocortisone initiation with respect to the onset of shock.

### OUTCOMES

The primary outcome measure was 90-day all-cause mortality. Secondary outcomes included all-cause mortality at ICU and hospital discharge at 28 days and at 180 days; resolution of organ failure (defined as a SOFA score <4); time to vasopressor withdrawal and cessation of mechanical ventilation; organ failure–, vasopressor-, and mechanical ventilation–free days (up to 28 days); length of stay in the ICU and in the hospital; superinfection (as defined by any new infection occurring >48 hours after randomization); and an episode of hyperglycemia or hypernatremia, gastroduodenal bleeding, and muscle weakness as defined in individual trials.

### RISK OF BIAS IN INDIVIDUAL STUDIES

Risk of bias was assessed independently by two authors (D.A. and A.D.) for each of the individual studies using a modified Cochrane risk of bias tool.[15] Any disputes were resolved by discussion or referral to a third adjudicator (F.L.).

### CERTAINTY OF EVIDENCE

A summary of the results is presented according to the recommendation of the Grading of Recommendations, Assessment, Development and Evaluation approach.[15] Five reviewers (R.P., D.A., A.D., A.G., and F.L.) rated each domain for each comparison separately and resolved discrepancies by consensus.

### STATISTICAL ANALYSIS

The primary analysis compared hydrocortisone versus placebo or usual care (control) in trial participants with septic

shock on all-cause mortality at 90 days. Patient-level data were aggregated, and the primary outcome was analyzed by using a one-stage meta-analysis by adopting a single mixed-effects logistic regression model that accounts for potential heterogeneity across studies. Treatment effect estimates were adjusted for study (random intercept) and the following variables collected at or before randomization: age, sex, predicted mortality obtained from the Simplified Acute Physiology Score II[12] or the Acute Physiology and Chronic Health Evaluation II,[13] SOFA score,[14] admission type (medical, elective surgery, or emergent surgery), infection site, infection type (hospital- vs. community-acquired infection), type of pathogen involved, baseline and increment in cortisol concentration post-corticotropin, mean arterial pressure, heart rate, lactate concentration, norepinephrine dose, ratio or arterial oxygen pressure to fraction of inspired oxygen ($PaO_2/FiO_2$), and treatment with mechanical ventilation. The following study-level characteristics were included in the models: fludrocortisone versus no fludrocortisone, steroid tapering versus no tapering, and steroid continuous infusion versus bolus (fixed effects). A random study-by-treatment interaction term was also included in the model.[16] Test for qualitative interaction between treatment effect and prespecified subgroups of interest was performed by using the Gail and Simon test.[17] Results are expressed as marginal relative risks (RRs) together with their 95% confidence intervals (CIs).[18]

### *Secondary Analyses*

Rates of day 28, day 180, ICU, and in-hospital mortality were analyzed by using a one-step mixed-effects logistic regression model. For cessation of vasopressor therapy, cessation of mechanical ventilation, and recovery from organ failure (defined by a SOFA score $<4$ for at least 24 hours), cumulative event incidences were estimated with death treated as a competing risk and compared by using the Fine and Gray test.[19] Lengths of stay were compared by using the Wilcoxon test. Adverse events were analyzed by using a one-step logistic regression model.

### *Sensitivity Analyses*

First, to account for potential complex interactions between covariates, we estimated the average treatment effect using the targeted maximum likelihood estimator, which uses machine learning to model the relationship between the outcome and the explanatory variables.[20] Second, a two-stage meta-analysis (i.e., a study-level meta-analysis) was used whereby the results obtained at the study level were combined by using a multilevel random effect meta-analysis approach. Studies with no individual data available were also included in this study-level meta-analysis. Results were illustrated by using forest plots. Publication bias was explored by using funnel plots and the Egger test. Although not prespecified, to include data from studies reporting mortality at a different time point than 90 days from randomization, we treated observations without actual information on survival status at day 90 as censored and used a Cox proportional-hazards mixed-effects model. Survival curves were generated by using the Kaplan–Meier estimator.

### *Fixed-Effect Network Meta-Analysis*

To simultaneously compare the different treatment protocols (hydrocortisone, hydrocortisone plus fludrocortisone, and continuous infusion vs. bolus), we performed a fixed-effects network meta-analysis. Treatment ranking was performed by using P scores derived from the point estimates and SEs of the frequentist network meta-analysis estimates. Using a scale of 0 to 1, they are used to measure the mean extent of certainty that a treatment is better than the competing treatments.

All analyses were performed on an intention-to-treat basis. Multilevel joint modeling multiple imputation was used to handle missing baseline data. Observations with missing outcome (death/alive status at the end of the follow-up) were included in the analysis. A sensitivity analysis was performed on complete cases owing to very few missing data for the primary outcome. We did not adjust for multiple comparisons. More details on the statistical analysis are provided in the Supplementary Appendix.

## Results

### STUDY SELECTION AND INDIVIDUAL PARTICIPANT DATA OBTAINED

There were 8928 unique reports of studies identified by the search; 24 met the inclusion criteria for this review, and 17 contributed individual patient data (n=7882 trial participants). Publication dates ranged from 1998 to 2019. The PRISMA flow diagram and reasons for exclusion are presented in Figure 1.

### CHARACTERISTICS OF THE INCLUDED STUDIES AND TRIAL PARTICIPANTS

The characteristics of the included and excluded studies are presented in Tables S1 and S2 in the Supplementary

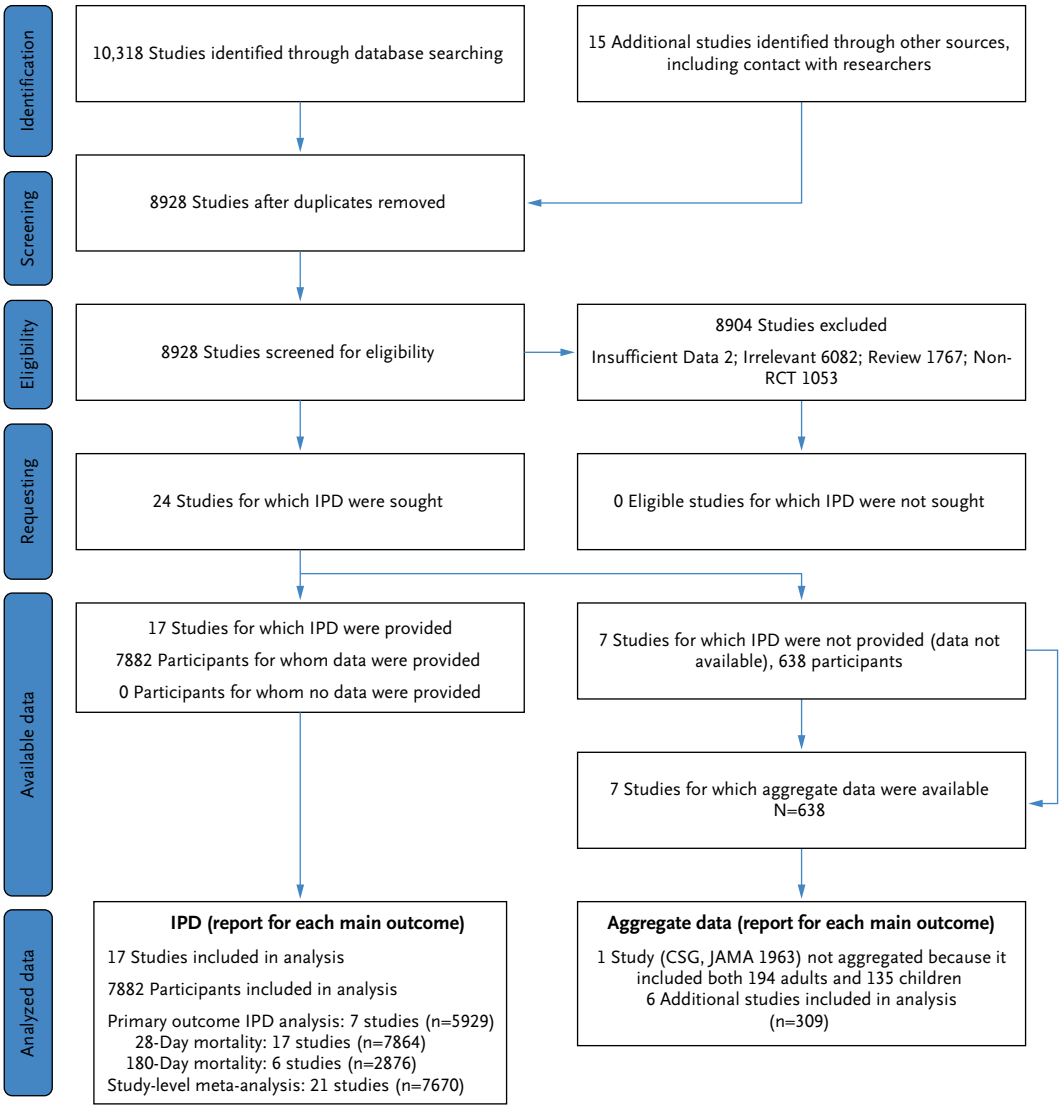



Figure 1. PRISMA Flow Diagram.

CSG denotes Cooperative Study Group; IPD, individual participant data; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; and RCT, randomized controlled trial.

Appendix. There were no major issues identified by integrity checks of the individual patient data, with full details of the reconciliation shown in Table S3. The baseline demographics and clinical characteristics of the participants included are shown in Table 1, with additional details from studies that did not provide individual patient data presented in Table S4.

## RISK OF BIAS WITHIN STUDIES

The results of the risk of bias assessment are given in Figures S1 and S2. For the seven studies that contributed individual patient data for the primary outcome, three were adjudicated as low risk of bias, and these included 5293 (91.8%) of all 5765 patients included in the primary analysis.

## PRIMARY OUTCOME

There were seven trials including participants that reported 90-day mortality in those with septic shock who were allocated to receive either hydrocortisone or control. Of the 5929 patients enrolled in these trials, 90-day mortality data were missing in 164 (2.8%). The estimated marginal RR for mortality for those allocated to receive hydrocortisone compared with control was 0.93 (95% CI, 0.82 to 1.04; P=0.22) (Table 2 and Fig. 2A). The mortality rates at

**Table 1. Baseline Characteristics according to Treatment Allocation.***

| Characteristic | Placebo (n=3624) | Hydrocortisone (n=4258) | Overall (N=7882) |
|---|---|---|---|
| Age — yr | 63 [54, 75] | 65 [54, 75] | 63 [54, 75] |
| No. missing data | 1 | 0 | 1 |
| Sex — male (%) | 2144/3385 (63) | 2518/4125 (61) | 4662/7410 (63) |
| Admission type (%) | | | |
| Medical | 2207/3233 (68) | 2271/3359 (68) | 4478/6592 (68) |
| Elective surgery | 173/3233 (5) | 166/3359 (5) | 339/6592 (5) |
| Urgent surgery | 853/3233 (26) | 922/3359 (27) | 1775/6592 (27) |
| Predicted mortality† — % | 26 [18, 46] | 29 [19, 51] | 28 [19, 51] |
| No. missing data | 205 | 226 | 431 |
| SOFA score at admission | 10 [8, 12] | 10 [8, 13] | 10 [8, 13] |
| No. missing data | 2116 | 2221 | 4337 |
| Arterial pressure at inclusion — mm Hg | 70 [65,76] | 70 [65,76] | 70 [65, 76] |
| No. missing data | 1068 | 1603 | 2701 |
| Septic shock‡ (%) | 3375/3624 (93) | 4012/4258 (94) | 7387/7882 (94) |
| Infection type (%) | | | |
| Hospital acquired | 558/1328 (42) | 932/1912 (49) | 1490/3240 (46) |
| Community acquired | 770/1328 (58) | 980/1912 (51) | 1750/3240 (54) |
| Infection site (%) | | | |
| Lung | 1074/3389 (32) | 1261/4001 (32) | 2335/7390 (32) |
| Gastrointestinal | 636/3389 (19) | 667/4001 (17) | 1313/7390 (18) |
| Bacteremia | 206/3389 (6) | 208/4001 (5) | 414/7390 (6) |
| Soft tissue | 126/3389 (4) | 151/4001 (4) | 277/7390 (4) |
| Urinary tract | 173/3389 (5) | 219/4001 (5) | 392/7390 (5) |
| Multiple | 975/3389 (29) | 1244/4001 (31) | 2219/7390 (30) |
| Others | 199/3389 (6) | 241/4001 (6) | 440/7390 (6) |
| Pathogen (%) | | | |
| Gram positive | 826/3428 (24) | 976/4045 (24) | 1802/7473 (24) |
| Gram negative | 803/3428 (23) | 1003/4045 (25) | 1806/7473 (24) |
| Others | 1799/3428 (53) | 2006/4045 (50) | 3865/7473 (52) |
| Lactate at inclusion — mmol/l | 3.87 [1.70, 4.70] | 3.9 [1.70, 4.90] | 3.93 [1.70, 4.80] |
| No. missing data | 144 | 195 | 339 |
| Cortisol at baseline (before stimulation, when available) — µg/L | 16.47 [9.21, 27] | 20.07 [11.56, 33.30] | 18.60 [10.4, 30.73] |
| No. missing data | 2550 | 2671 | 5221 |
| Cortisol after corticotropin stimulation (when available) — µg/L | 21.24 [11.95, 35.30] | 26.44 [14.50, 42.38] | 24.00 [13.39, 40.34] |
| No. missing data | 2575 | 2768 | 5343 |
| Norepinephrine equivalent at inclusion — µg/kg/min | 0.23 [0.10, 0.63] | 0.24 [0.10, 0.63] | 0.24 [0.10, 0.63] |
| No. missing data | 716 | 866 | 1582 |
| Mechanical ventilation (%) | 3151/3430 (92) | 3733/4006 (93) | 6884/7436(93) |

* All continuous variables are reported as median [1st, 3rd quartile]. Categorical variables are presented as absolute number (percentage). SOFA denotes Sequential Organ Failure Assessment.

† Predicted mortality is based on the severity score available.

‡ Septic shock as defined in original studies.

each time point are shown in Table S5. The certainty of evidence was judged to be moderate (Table 3). The results of the prespecified sensitivity analyses are shown in Table 2 and Figure S3. The post hoc survival analysis found a hazard ratio of 0.92 (95% CI, 0.81 to 1.05) (Table 2 and Fig. S4). In the network meta-analysis, hydrocortisone plus fludrocortisone was ranked best therapy (P score=0.959), and with the control group as the reference group,

| Table 2. Primary and Secondary Outcomes and Adverse Events.* | | | | | |
|---|---|---|---|---|---|
| **Outcome** | **Trials** | **Participants** | **Estimate of Effect†** | **95% CI** | **P Value** |
| Primary outcome: 90-day all-cause mortality | | | | | |
| Adjusted RR | 7 | 5929 | 0.93 | 0.82 to 1.04 | 0.22 |
| Unadjusted RR | 7 | 5929 | 0.95 | 0.89 to 1.02 | 0.21 |
| TMLE | 7 | 5029 | 0.96 | 0.90 to 1.02 | 0.21 |
| Cox model — marginal hazard ratio | 17 | 7873 | 0.92 | 0.81 to 1.05 | 0.27 |
| Trial level meta-analysis — RR | 21 | 7670 | 0.93 | 0.86 to 1.01 | 0.11 |
| Including patient with sepsis‡ — RR | 8 | 6138 | 0.95 | 0.88 to 1.02 | 0.24 |
| Secondary outcomes | | | | | |
| Mortality at day 28 — RR | 17 | 7864 | 0.92 | 0.83 to 1.00 | — |
| Mortality at day 180 — RR | 6 | 1997 | 0.92 | 0.74 to 1.10 | — |
| Mortality at ICU discharge — RR | 12 | 7314 | 0.92 | 0.83 to 1.01 | — |
| Mortality at hospital discharge — RR | 10 | 6676 | 0.95 | 0.88 to 1.03 | — |
| Vasopressor-free days§ — MD | 13 | 6422 | 1.24 | 0.74 to 1.73 | — |
| Ventilation-free days§ — MD | 15 | 7061 | 0.46 | −0.08 to 0.99 | — |
| Organ failure–free days§ — MD | 12 | 1082 | 0.27 | −0.65 to 0.92 | — |
| Duration of ICU admission — MD, d | 15 | 7636 | 0.13 | −0.65 to 0.92 | — |
| Duration of hospital admission — MD, d | 14 | 7591 | 0.22 | −1.17 to 1.62 | — |
| Adverse events | | | | | |
| Superinfection | 10 | 6970 | 1.04 | 0.95 to 1.15 | |
| Hyperglycemia | 10 | 7017 | 1.05 | 0.98 to 1.12 | |
| Hypernatremia | 6 | 5033 | 2.01 | 1.56 to 2.60 | |
| Gastroduodenal bleeding | 8 | 2748 | 1.11 | 0.83 to 1.48 | |
| Muscle weakness | 5 | 2647 | 1.73 | 1.49 to 1.99 | |

* The widths of the CIs have not been adjusted for multiplicity. Thus, the CIs should not be used to reject or not reject treatment effects. CI denotes confidence interval; ICU, intensive care unit; MD, mean difference; RR, relative risk; and TMLE, targeted maximum likelihood estimation.

† Estimates of effects are marginal risk ratio unless indicated.

‡ Patients with sepsis but no shock.

§ Vasopressor-, ventilation-, and organ failure–free days are calculated up to day 28.

hydrocortisone plus fludrocortisone was associated with reduced 90-day all-cause mortality compared with control (fixed-effect RR, 0.88; 95% CI, 0.81 to 0.97; moderate certainty) (Fig. S5).

## SECONDARY OUTCOMES

The results of the secondary outcomes are shown in Table 2 and Table S5. Trial participants allocated to receive hydrocortisone had more days alive and free of vasopressor treatment compared with those allocated to control (estimated adjusted mean difference, 1.24 days; 95% CI, 0.74 to 1.73) (Table S5 and Fig. S6). Days alive and free of mechanical ventilation, days alive and free of organ failure, and duration of ICU and hospital stay were similar in the two groups.

## ADVERSE EVENTS

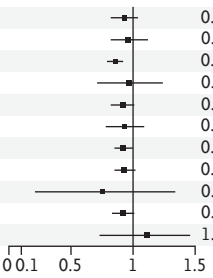
The incidences of specified adverse events are shown in Table 2 and Table S5. Hydrocortisone may be associated with an increase in the risk of hypernatremia (RR, 2.01; 95% CI, 1.56 to 2.60; low certainty) and of muscle weakness (n=2647; RR, 1.73; 95% CI, 1.49 to 1.99; low certainty) but not of superinfection (RR, 1.04; 95% CI, 0.95 to 1.15; low certainty), hyperglycemia (RR, 1.05; 95% CI, 0.98 to 1.12; low certainty), or gastroduodenal bleeding (RR, 1.11;95% CI, 0.83 to 1.48; low certainty).

## SECONDARY ANALYSES

The results of subgroup analyses based on differences in the delivery of the intervention are shown in Figure 2A. The RR for 90-day mortality was 0.86 (95% CI, 0.79 to 0.92) for hydrocortisone plus fludrocortisone compared with control and 0.96 (95% CI, 0.82 to 1.12) for hydrocortisone without fludrocortisone compared with control (test for interaction, P=0.01). There was no evidence of a differential effect of hydrocortisone compared with control on 90-day mortality in subgroups defined by whether the

**A**

| Treatment | Subgroup | Total No. of Patients (treatment+ control) (%) | No. Treated (%) | No. of Deaths in Treated (%) | No. Placebo (%) | No. of Deaths in Placebo (%) | Relative Risk (CI) |
|---|---|---|---|---|---|---|---|
| Overall | | 5929 (100)* | 2966 (100) | 1026 (36) | 2963 (100) | 1069 (37) | 0.93 (0.82–1.04) |
| Hydrocortisone | Without fludrocortisone | 4389 (74) | 2202 (74) | 665 (31) | 2187 (74) | 656 (31) | 0.96 (0.82–1.12) |
| | With fludrocortisone | 1540 (26) | 764 (26) | 361 (47) | 776 (26) | 413 (53) | 0.86 (0.79–0.92) |
| Taper | Taper | 657 (11) | 329 (11) | 135 (51) | 328 (11) | 127 (49) | 0.97 (0.71–1.24) |
| | No taper | 5272 (89) | 2637 (89) | 891 (34) | 2635 (89) | 942 (36) | 0.92 (0.82–1.01) |
| Continuous | Continous | 3844 (65) | 1922 (65) | 538 (29) | 1922 (65) | 552 (30) | 0.93 (0.78–1.09) |
| | Bolus | 2085 (35) | 1044 (35) | 488 (48) | 1041 (35) | 517 (51) | 0.92 (0.85–1.00) |
| Steroid duration | Fixed | 5771 (97) | 2888 (97) | 999 (35) | 2883 (97) | 1043 (37) | 0.93 (0.85–1.02) |
| | Shock reversal | 158 (3) | 78 (3) | 27 (60) | 80 (3) | 26 (63) | 0.75 (0.21–1.34) |
| Steroid initiation | <24 h | 5723 (97) | 2865 (97) | 982 (35) | 2858 (97) | 10,255 (37) | 0.92 (0.83–1.01) |
| | >24 h | 176 (3) | 85 (3) | 40 (56) | 91 (3) | 39 (50) | 1.11 (0.73–1.46) |




**B**

| Variable | Subgroup | No. of Patients (%) | No. Treated (%) | No. of Deaths in Treated (%) | No. Placebo (%) | No. of Deaths in Placebo (%) | Relative Risk (CI) |
|---|---|---|---|---|---|---|---|
| Overall | | 5929 (100)* | 2966 (100) | 1026 (36) | 2963 (100) | 1069 (37) | 0.93 (0.82–1.04) |
| Age — yr | <54 | 1485 (25) | 755 (25) | 169 (23) | 729 (25) | 157 (22) | 0.97 (0.79–1.18) |
| | 54–65 | 1405 (24) | 713 (24) | 214 (31) | 692 (23) | 227 (34) | 0.90 (0.70–1.12) |
| | 65–74 | 1446 (24) | 730 (25) | 258 (36) | 716 (24) | 287 (41) | 0.86 (0.68–1.07) |
| | >74 | 1592 (27) | 768 (26) | 385 (51) | 824 (28) | 398 (50) | 1.00 (0.88–1.13) |
| Sex | Female | 2202 (37) | 1126 (38) | 379 (35) | 1076 (36) | 351 (34) | 0.99 (0.84–1.14) |
| | Male | 3725 (63) | 1840 (62) | 647 (36) | 1885 (64) | 718 (39) | 0.90 (0.78–1.02) |
| Mortality — % | <17.6 | 1413 (24) | 694 (24) | 103 (15) | 719 (25) | 143 (20) | 0.90 (0.66–1.20) |
| | 17.6–24.7 | 1325 (23) | 662 (23) | 181 (28) | 663 (23) | 198 (30) | 0.88 (0.67–1.12) |
| | 24.7–41.9 | 1643 (28) | 834 (29) | 306 (37) | 809 (28) | 306 (39) | 0.92 (0.76–1.09) |
| | >41.9 | 1461 (25) | 728 (25) | 412 (58) | 733 (25) | 418 (59) | 0.98 (0.86–1.10) |
| SOFA score | <9 | 369 (18) | 167 (17) | 52 (34) | 202 (20) | 76 (42) | 0.98 (0.75–1.22) |
| | 9–11 | 455 (23) | 210 (21) | 81 (41) | 245 (24) | 88 (39) | 0.92 (0.67–1.21) |
| | 11–13 | 529 (26) | 264 (27) | 112 (45) | 265 (26) | 136 (53) | 0.92 (0.71–1.14) |
| | >13 | 669 (33) | 352 (35) | 205 (60) | 317 (31) | 203 (66) | 0.96 (0.83–1.09) |
| Cortisol increment after 250 μg of ACTH — μd/dl | ≥9 | 428 (7) | 225 (8) | 95 (45) | 203 (7) | 80 (43) | 1.04 (0.85–1.25) |
| | <9 | 5497 (93) | 2740 (92) | 931 (35) | 2757 (93) | 989 (37) | 0.92 (0.82–1.02) |
| Infection type | Hospital | 786 (36) | 397 (36) | 197 (55) | 389 (36) | 189 (54) | 0.99 (0.85–1.11) |
| | Community | 1395 (64) | 699 (64) | 302 (45) | 696 (64) | 344 (51) | 0.90 (0.75–1.05) |
| Admission | Medical | 3844 (67) | 1943 (67) | 707 (37) | 1941 (67) | 724 (38) | 0.94 (0.85–1.04) |
| | Surgical | 1884 (33) | 941 (33) | 284 (31) | 943 (33) | 317 (34) | 0.89 (0.74–1.05) |
| Site | Lung | 1701 (29) | 833 (28) | 310 (38) | 868 (30) | 334 (39) | 0.92 (0.79–1.05) |
| | Else | 4138 (71) | 2091 (72) | 702 (34) | 2047 (70) | 720 (36) | 0.93 (0.82–1.05) |
| Pathogen | Gram negative | 1488 (25) | 748 (25) | 246 (33) | 740 (25) | 246 (34) | 0.92 (0.75–1.11) |
| | Gram positive | 1364 (23) | 694 (24) | 240 (36) | 670 (23) | 238 (37) | 0.91 (0.74–1.11) |
| | Other | 2999 (52) | 1507 (51) | 531 (36) | 1492 (52) | 565 (38) | 0.91 (0.82–1.01) |
| Sepsis–3 | Yes | 3827 (68) | 1888 (67) | 745 (40) | 1939 (68) | 776 (41) | 0.96 (0.86–1.06) |
| | No | 1831 (32) | 930 (33) | 224 (25) | 901 (32) | 245 (28) | 0.87 (0.75–1.01) |
| Etomidate | Yes | 177 (3) | 88 (3) | 48 (58) | 89 (3) | 53 (64) | 0.99 (0.59–1.29) |
| | No | 5497 (97) | 2747 (97) | 912 (34) | 2750 (97) | 970 (36) | 0.92 (0.83–1.02) |
| Lactate — mmol/l | <1.7 | 1359 (24) | 676 (24) | 152 (23) | 683 (24) | 180 (27) | 0.86 (0.74–1.00) |
| | 1.7–2.8 | 1456 (26) | 743 (26) | 229 (32) | 713 (25) | 223 (32) | 0.94 (0.76–1.15) |
| | 2.8–5 | 1434 (25) | 686 (24) | 228 (34) | 748 (26) | 275 (38) | 0.92 (0.74–1.10) |
| | >5 | 1409 (25) | 713 (25) | 360 (52) | 696 (25) | 343 (51) | 0.99 (0.83–1.13) |
| Norepinephrine — μg/kg/min | <0.11 | 1328 (24) | 660 (24) | 147 (23) | 668 (24) | 157 (24) | 0.94 (0.72–1.20) |
| | 0.11–0.23 | 1330 (24) | 667 (24) | 166 (25) | 663 (24) | 170 (26) | 0.95 (0.73–1.19) |
| | 0.23–0.60 | 1399 (26) | 700 (26) | 247 (36) | 699 (26) | 261 (39) | 0.92 (0.76–1.10) |
| | >0.60 | 1412 (26) | 706 (26) | 337 (49) | 706 (26) | 361 (53) | 0.91 (0.77–1.05) |
| Vasopressin | Yes | 607 (13) | 284 (12) | 90 (32) | 323 (13) | 112 (35) | 0.93 (0.72–1.18) |
| | No | 4241 (87) | 2141 (88) | 661 (31) | 2100 (87) | 692 (33) | 0.92 (0.81–1.05) |

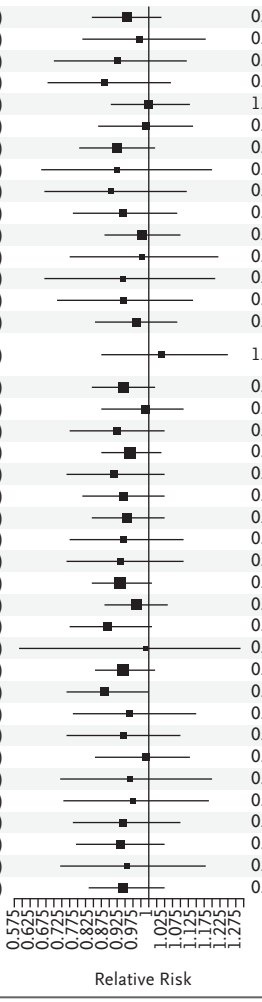



Figure 2. Forest Plot for the Association between Steroid and 90-Day Mortality.

Subgroups defined according to study-level characteristics (Panel A) and overall (Panel B). Population and subgroups defined according to patient-level characteristics. The widths of the CIs have not been adjusted for multiplicity. Thus, the CIs should not be used to reject or not reject treatment effects. *The total number of patients, the number of patients in the treated group, and the placebo group are based on the total number of patients included in the primary analysis (i.e., including the 164 patients with a missing outcome at day 90). The number of deaths in the treated and the placebo groups is based on the 5765 patients with a reported outcome at day 90. ACTH denotes adrenocorticotropic hormone; CIs, confidence intervals; Sepsis-3, Third International Consensus Definitions for Sepsis and Septic Shock; and SOFA, Sequential Organ Failure Assessment.

**Table 3. Summary of Findings.***

| Certainty Assessment | | | | | | | No. of Patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of studies | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | Hydrocortisone | Placebo | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| 90-day mortality (follow-up, 90 days) | | | | | | | | | | | | |
| 7 | Randomized trials | Not serious | Not serious | Not serious | Serious† | None | 1026/2888 (35.5%) | 1069/2877 (37.2%) | RR 0.93 (0.82 to 1.04) | 26 fewer per 1000 (from 64 fewer to 15 more) | ⊕⊕⊕◯ Moderate | Critical |
| 28-day mortality (follow-up, 28 days) | | | | | | | | | | | | |
| 17 | Randomized trials | Not serious | Not serious | Not serious | Serious† | None | 1255/4248 (29.5%) | 1055/3616 (29.2%) | RR 0.92 (0.83 to 1.00) | 23 fewer per 1000 (from 50 fewer to 0 more) | ⊕⊕⊕◯ Moderate | Critical |
| 180-day mortality (follow-up, 180 days) | | | | | | | | | | | | |
| 6 | Randomized trials | Serious‡ | Not serious | Not serious | Serious† | None | 487/999 (48.7%) | 527/998 (52.8%) | RR 0.92 (0.74 to 1.10) | 40 fewer per 1000 (from 130 fewer to 50 more) | ⊕⊕◯◯ Low | Critical |
| Vasopressor-free days (follow-up, 28 days) | | | | | | | | | | | | |
| 13 | Randomized trials | Not serious | Not serious | Not serious | Not serious | None | 3456 | 2996 | — | MD 1.24 days higher (0.74 higher to 1.73 higher) | ⊕⊕⊕⊕ High | Important |
| Superinfections (follow-up range, 28–180 days) | | | | | | | | | | | | |
| 10 | Randomized trials | Not serious | Serious§ | Not serious | Serious† | None | 737/3762 (19.6%) | 602/3208 (18.8%) | RR 1.04 (0.95 to 1.15) | 8 more per 1000 (from 9 fewer to 28 more) | ⊕⊕◯◯ Low | Important |
| Muscular weakness (follow-up range, 28–180 days) | | | | | | | | | | | | |
| 5 | Randomized trials | Not serious | Serious¶ | Not serious | Serious† | None | 451/1601 (28.2%) | 171/1046 (16.3%) | RR 1.73 (1.49 to 1.99) | 119 more per 1000 (from 80 more to 162 more) | ⊕⊕◯◯ Low | Important |

* Numbers of patients are based on participants for whom the outcome was not missing. CI denotes confidence interval; MD, mean difference; and RR, relative risk.

† Most trials did not report this outcome.

‡ Inconsistent results between trials.

§ Wide CIs.

¶ Heterogeneous or unclear definitions.

hydrocortisone was tapered or abruptly discontinued, whether it was given as an infusion or as bolus doses, whether it was given for a fixed duration or for the duration of shock, or whether it was initiated within 24 hours or after 24 hours of shock onset.

### SUBGROUP ANALYSES

The results of subgroup analyses based on patient-level characteristics are presented in Figure 2B. There was no significant differential treatment effect in the patient-level subgroups. We could not collect data for the prespecified subgroups based on an individual component of the SOFA score on the appropriateness of antibiotic therapy or on the presence of preexisting conditions likely to be associated with an altered hypothalamic-pituitary axis or renin-angiotensin-aldosterone axis.

## Discussion

This patient-level meta-analysis of hydrocortisone for patients with septic shock found that hydrocortisone was not associated with reduced risk of 90-day all-cause mortality. The effects of hydrocortisone on 90-day all-cause mortality did not differ significantly between continuous versus bolus administration, a fixed-duration versus vasopressor dependency–guided administration, or between discontinuation with tapering versus without tapering. Hydrocortisone may be associated with a decreased risk of ICU mortality and with increased vasopressor-free days but may not be associated with reduced mortality at 28 days, 180 days, and hospital discharge. Hydrocortisone may be associated with an increased risk of muscle weakness.

Two trials reported reduced mortality with hydrocortisone plus fludrocortisone in adults with septic shock.[4,21] In this patient-level meta-analysis, there was a statistically significant interaction between enteral administration of fludrocortisone and response to hydrocortisone. In a network meta-analysis, hydrocortisone plus fludrocortisone was ranked best therapy (P score=0.964). These trials have included more severely ill patients than the other trials. Nevertheless, the current meta-analysis was adjusted on the severity of illness score–based predicted mortality, lactate levels, and level of vasopressor dependency.

This patient-level meta-analysis investigated the effects of hydrocortisone across several subgroups based on patient-level characteristics to inform the design of future trials. We found no patient characteristic at baseline discriminating responders and nonresponders to hydrocortisone. It is now recognized that patients with sepsis may have similar clinical and physiological characteristics but differ in genetic background and immunologic responses that influence the course of illness, prognosis, and response to treatment. Response to glucocorticoids in critically ill patients may be variable. Acute stress can alter either glucocorticoid receptor-α function or glucocorticoid receptor-α expression with a decrease in glucocorticoid sensitivity and, ultimately, glucocorticoid resistance.[22] Differences in sepsis-induced genomewide expression patterns may affect mortality, as evidenced by the observation that an immunocompetent phenotype might be associated with higher mortality when treated with glucocorticoids than those with an immune-suppressed expression phenotype.[23] These findings serve to highlight the clinical and biological heterogeneity of septic shock. Innovative biomarkers could be more useful in identifying individual patients who may benefit from corticosteroid therapy. Individual treatment rules based on machine learning[24] or omics profiling could pave the way for personalized treatment approaches.[25-27]

The strengths of the current study include a predefined protocol and a statistical analysis plan, a comprehensive literature search, a list of excluded studies with justifications, and a fair representativeness of the global population with septic shock (Table S6). Study limitations include a 20-year period between the first and last published trials with changes in clinical practices. To limit this bias, we used covariate adjustments to capture any potential source of variability related to the time a study was conducted. Individual patient data were available in 17 trials, and all-cause 90-day mortality data were available for only seven of these trials. The aggregated data from all studies were included in the study-level meta-analysis whose results were consistent with those of the patient-level analysis. The results of subgroup analysis should be interpreted with caution owing to the number of subgroups and the potential of insufficient power. The analysis is also limited by the underlying internal and external validity of the included trials. Results on complications should be interpreted with caution since information on complications was only available for a limited number of patients. Finally, although the Egger test was not significant, some degree of publication bias is possible.

In conclusion, in adults with septic shock, hydrocortisone is not associated with a significant decrease in 90-day all-cause mortality.

## Disclosures

Author disclosures and other supplementary materials are available at www.evidence.nejm.org.

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