The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2018 VOL. 378 NO. 9

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS

We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

RESULTS

From March 2013 through April 2017, a total of 3800 patients underwent randomization. Status with respect to the primary outcome was ascertained in 3658 patients (1832 of whom had been assigned to the hydrocortisone group and 1826 to the placebo group). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P=0.50). The effect of the trial regimen was similar in six prespecified subgroups. Patients who had been assigned to receive hydrocortisone had faster resolution of shock than those assigned to the placebo group (median duration, 3 days [interquartile range, 2 to 5] vs. 4 days [interquartile range, 2 to 9]; hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001). Patients in the hydrocortisone group had a shorter duration of the initial episode of mechanical ventilation than those in the placebo group (median, 6 days [interquartile range, 3 to 18] vs. 7 days [interquartile range, 3 to 24]; hazard ratio, 1.13; 95% CI, 1.05 to 1.22; P<0.001), but taking into account episodes of recurrence of ventilation, there were no significant differences in the number of days alive and free from mechanical ventilation. Fewer patients in the hydrocortisone group than in the placebo group received a blood transfusion (37.0% vs. 41.7%; odds ratio, 0.82; 95% CI, 0.72 to 0.94; P=0.004). There were no significant between-group differences with respect to mortality at 28 days, the rate of recurrence of shock, the number of days alive and out of the ICU, the number of days alive and out of the hospital, the recurrence of mechanical ventilation, the rate of renal-replacement therapy, and the incidence of new-onset bacteremia or fungemia.

CONCLUSIONS

Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo. (Funded by the National Health and Medical Research Council of Australia and others; ADRENAL ClinicalTrials.gov number, NCT01448109.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Venkatesh at the Department of Intensive Care, Wesley Hospital, 451 Coronation Dr., Auchenflower, Brisbane, QLD 4066, Australia, or at bvenkatesh@georgeinstitute.org.au.

*A full list of investigators in the ADRENAL Trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on January 19, 2018, at NEJM.org.

N Engl J Med 2018;378:797-808.
DOI: 10.1056/NEJMoa1705835

Sepsis, which has been identified by the World Health Organization as a global health priority, has no proven pharmacologic treatment, other than the appropriate antibiotic agents, fluids, and vasopressors as needed; reported death rates among hospitalized patients range between 30% and 45%.[1-6] Glucocorticoids have been used as an adjuvant therapy for septic shock for more than 40 years.[7] Nonetheless, uncertainty about their safety and efficacy remains.

Randomized, controlled trials that were conducted in the 1980s showed that the use of high-dose methylprednisolone (30 mg per kilogram of body weight) was associated with higher morbidity and mortality than control.[8,9] Two randomized, controlled trials that examined the effect of lower-dose hydrocortisone (200 mg per day) on mortality among patients with septic shock showed conflicting results,[10,11] although each trial showed an earlier reversal of shock in patients who had been treated with hydrocortisone than in control patients.

Subsequent systematic reviews and meta-analyses have not provided compelling evidence for or against the use of hydrocortisone in patients with septic shock.[12-14] Current clinical practice guidelines recommend the use of hydrocortisone in patients with septic shock if adequate fluid resuscitation and treatment with vasopressors have not restored hemodynamic stability; however, the guidelines classify the recommendation as weak, on the basis of the low quality of available evidence.[15]

The uncertainty about the efficacy of glucocorticoids in reducing mortality among patients with septic shock has resulted in widespread variation in clinical practice.[16] Reports of potential adverse effects associated with glucocorticoids, including superinfection and metabolic and neuromuscular effects, have compounded clinical uncertainty.[11] We designed the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial to test the hypothesis that hydrocortisone results in lower mortality than placebo among patients with septic shock.[17]

Methods

Trial Design and Oversight

Our trial was an investigator-initiated, international, pragmatic, double-blind, parallel-group, randomized, controlled trial that compared intravenous infusions of hydrocortisone with matched placebo in patients with septic shock who were undergoing mechanical ventilation in an intensive care unit (ICU). We conducted the trial in Australia, the United Kingdom, New Zealand, Saudi Arabia, and Denmark.

The trial management committee designed the trial. The trial sponsor (the George Institute for Global Health, Australia) coordinated all the operational processes and conducted all the statistical analyses. Trained research coordinators collected data at each site and entered the information into a Web-based database. Data monitoring and source-data verification were conducted according to a prespecified monitoring plan (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Before enrollment was completed, we published the trial protocol (available at NEJM.org) and statistical analysis plan.[17,18] Approval from a human research ethics committee was obtained for all the sites before enrollment of the patients. Previous written informed consent or written consent to continue was obtained for all participants, according to the legal requirements in each jurisdiction. The authors vouch for the accuracy and completeness of the data and statistical analyses and for the fidelity of the trial to the protocol.

Neither Pfizer (which supplied hydrocortisone) nor Radpharm Scientific (which supplied placebo) had any input into the design or conduct of the study, data collection, statistical analysis, or writing of the manuscript. Mater Pharmacy Services (Brisbane, Australia) was responsible for acquisition of the drugs and the blinding processes. There was no contractual arrangement between the trial sponsor, the George Institute for Global Health, and either Pfizer or Radpharm Scientific. All contractual arrangements were between Mater Pharmacy Services and the George Institute for Global Health.

Patients

Eligible participants were adults (≥18 years of age) who were undergoing mechanical ventilation, for whom there was a documented or strong clinical suspicion of infection, who fulfilled two or more criteria of the systemic inflammatory response syndrome,[19] and who had been treated with vasopressors or inotropic agents for a minimum of 4 hours up to and at the time of ran-

domization. Patients were excluded if they were likely to receive treatment with systemic glucocorticoids for an indication other than septic shock, had received etomidate[20] (a short-acting anesthetic agent with adrenal-suppressant properties) during the current hospital admission, were considered to be likely to die from a preexisting disease within 90 days after randomization or had treatment limitations in place, or had met all the inclusion criteria for more than 24 hours. Detailed inclusion and exclusion criteria and the alignment of these criteria with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[21] are provided in Tables S2A through S2C in the Supplementary Appendix.

RANDOMIZATION AND TRIAL REGIMEN

We concealed the randomized trial-group assignments using a minimization algorithm by means of a password-protected, encrypted, Web-based interface. Randomization was stratified according to participating center and according to medical or surgical admission. Surgical admissions were defined as patients being admitted to the ICU from the operating room or the recovery room; all other admissions were considered to be medical admissions.

Patients were assigned to receive an intravenous infusion of hydrocortisone (Pfizer) at a dose of 200 mg per day or matching placebo (Radpharm Scientific). Blinding regarding the trial regimen was ensured by the supply of hydrocortisone and placebo in identical, masked vials. The integrity of the trial-group assignment was confirmed by an independent person who assessed a random sample of hydrocortisone and placebo packs from 10% of the trial population (Table S3A in the Supplementary Appendix). The trial regimen was reconstituted to produce a concentration of 1 mg per milliliter of hydrocortisone or an equivalent volume (in milliliters) of placebo. The trial dose volume was set at 200 ml, which was administered by means of continuous intravenous infusion over a period of 24 hours for a maximum of 7 days or until ICU discharge or death, whichever occurred first. A description of the blinding process and of the preparation and reconstitution of the trial regimen is provided in Table S3B in the Supplementary Appendix.

The patients, treating clinicians, and trial personnel were unaware of the trial-group assignments and sequence. All other aspects of the patients' care were conducted at the discretion of the treating clinicians.

OUTCOMES

The primary outcome was death from any cause at 90 days after randomization. Secondary outcomes included death from any cause at 28 days after randomization, the time to the resolution of shock,[22] the recurrence of shock, the length of ICU stay, the length of hospital stay, the frequency and duration of mechanical ventilation, the frequency and duration of treatment with renal-replacement therapy, the incidence of new-onset bacteremia or fungemia between 2 and 14 days after randomization, and the receipt of blood transfusion in the ICU. Definitions of the secondary outcomes are provided in Table S4 in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that a population of 3800 patients would provide the trial with 90% power to detect an absolute difference of 5 percentage points in 90-day all-cause mortality from an estimated baseline mortality of 33%, at an alpha level of 0.05.[6] This calculation allowed for a rate of withdrawal and loss to follow-up of 1%.

The primary-outcome result is presented as the odds ratio for death, with corresponding 95% confidence intervals, analyzed with the use of a logistic-regression model with adjustment for stratification variables, with admission type (medical or surgical) as a fixed effect and trial site as a random effect. Additional sensitivity analyses were performed by adding the following covariates to the main logistic-regression model: sex; age; Acute Physiology and Chronic Health Evaluation (APACHE) II score, assessed on a scale from 0 to 71, with higher scores indicating a higher risk of death[23]; the time from the onset of shock to randomization; and the use of renal-replacement therapy in the 24 hours before randomization.

The primary outcome was also examined in six prespecified subgroups, which were defined according to the following baseline characteristics: admission type (medical vs. surgical); dose of catecholamine infusions (norepinephrine or epinephrine at a dose of <15 μg per minute vs. ≥15 μg per minute); primary site of sepsis (pulmonary vs. nonpulmonary); sex (male vs. female); APACHE II score (<25 vs. ≥25; a score of ≥25 has

been used as a cutoff point to identify patients at a higher risk for death[24,25]); and the duration of shock according to four intervals of 6 hours each between 0 and 24 hours before randomization (<6 hours, 6 to 12 hours, 12 to 18 hours, or 18 to 24 hours). The secondary binary and continuous outcomes were analyzed with the use of logistic regression and linear regression, respectively, with adjustment for stratification variables. The rate of death in a time-to-event analysis was reported with the use of Kaplan–Meier plots, and differences in survival were tested with the use of a Cox proportional-hazards model[26] that included the randomized trial group, admission type, and a random effect for trial site.

The times to the resolution of shock and ventilation and the times to discharge from the ICU and the hospital were analyzed by means of two approaches: with death treated as a competing risk[27] and with results described with the use of cumulative incidence function; and as a post hoc analysis with data from patients censored at the time of death and with results described with the use of Kaplan–Meier plots. Differences in the time to event (e.g., resolution of shock, cessation of ventilation, and ICU or hospital discharge) were tested with the use of the same Cox model that was used for the analysis of time to death.

Physiological data were averaged over the period of days 1 to 14 and compared with the use of a repeated-measure, linear mixed model and were presented as overall mean differences with corresponding 95% confidence intervals. Post hoc analyses were performed with the use of a separate calculation of the mean differences over the period of days 1 to 7 (duration of trial regimen) and days 8 to 14. The proportions of patients who had adverse events and serious adverse events were compared with the use of Fisher's exact test.

All the analyses were conducted on an intention-to-treat basis with no imputation of missing data. For secondary outcomes, a post hoc Holm–Bonferroni procedure was applied to control for multiple testing.[28] All the analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

Two prespecified interim analyses were performed by an independent statistician when 950 patients (25%) and 2500 patients (66%) could be assessed with regard to the primary outcome at 90 days. These analyses were reviewed by an independent data monitoring committee.

RESULTS

PATIENTS

From March 2013 through April 2017, we identified 5501 eligible patients, of whom 3800 were enrolled in the trial at 69 medical–surgical ICUs. The ICUs were in Australia (45 sites), the United Kingdom (12), New Zealand (8), Saudi Arabia (3), and Denmark (1).

Of the 3800 patients enrolled, 1898 were assigned to receive hydrocortisone and 1902 to receive placebo. A total of 114 patients (3.0%) either withdrew (24 patients) or did not have informed consent obtained (90), and 28 of the remaining 3686 patients (0.8%) were lost to follow-up at 90 days. Thus, the trial included 3658 enrolled patients, of whom 1832 in the hydrocortisone group and 1826 in the placebo group were included in the analysis of the primary outcome (Figs. S1 and S2 and Table S5 in the Supplementary Appendix).

The characteristics of the patients at baseline were similar in the two groups (Table 1). The mean (±SD) age of the patients was 62.3±14.9 years in the hydrocortisone group and 62.7±15.2 years in the placebo group; the percentages of male patients were 60.4% and 61.3%, respectively; the median APACHE II scores were 24.0 (interquartile range, 19.0 to 29.0) and 23.0 (interquartile range, 18.0 to 29.0), respectively; and the percentages of patients with surgical admission were 31.2% and 31.8%, respectively. The primary site of infection was similar in the two groups and was predominantly of pulmonary origin among patients with a medical diagnosis and of abdominal origin among patients with a surgical admission (Tables S6 and S7 in the Supplementary Appendix).

TRIAL AND CONCOMITANT REGIMENS

The assigned trial regimen was received by 1834 of 1837 patients (99.8%) in the hydrocortisone group and by 1838 of 1843 (99.7%) in the placebo group. The median time from randomization to the commencement of the trial regimen was 0.8 hours (interquartile range, 0.4 to 1.6) in the hydrocortisone group and 0.8 hours (interquartile range, 0.4 to 1.5) in the placebo group

(P=0.28). There was no significant between-group difference in the cumulative duration of the trial regimen (median, 5.1 days [interquartile range, 2.7 to 6.8] in the hydrocortisone group and 5.6 days [interquartile range, 2.9 to 6.8] in the placebo group; P=0.09). The overall mean rate of adherence to the dosing protocol was 95.2±11.3% in the hydrocortisone group and 94.9±12.1% in the placebo group (P=0.34) (Table S8 and Fig. S3 in the Supplementary Appendix).

Between days 1 and 14 after randomization, 138 of 1853 patients (7.4%) in the hydrocortisone group and 164 of 1860 (8.8%) in the placebo group received open-label glucocorticoids (P=0.13). The use of inotropes, vasopressors, etomidate, statins, and antimicrobial therapies did not differ significantly between the groups (Tables S8 and S9 in the Supplementary Appendix).

Between days 1 and 7, patients in the hydrocortisone group had a higher mean arterial pressure than did those in the placebo group (difference, 5.39 mm Hg; P<0.001), as well as a higher plasma lactate level (difference, 0.08 mmol per liter; P=0.02) and a lower heart rate (difference, −6.6 beats per minute; P<0.001). There were no significant between-group differences in the daily peak dose of norepinephrine among patients who were receiving vasopressors between days 1 and 14. (Details are provided in Fig. S4A through S4E in the Supplementary Appendix.)

PRIMARY OUTCOME

At 90 days after randomization, 511 of 1832 patients (27.9%) who had been assigned to receive hydrocortisone had died, as had 526 of 1826 (28.8%) who had been assigned to receive placebo (odds ratio, 0.95; 95% confidence interval [CI], 0.82 to 1.10; P=0.50) (Table 2, and Table S10 and Fig. S5 in the Supplementary Appendix). There was no significant between-group difference in the rate of death in the time-to-event analysis during the 90 days after randomization (hazard ratio, 0.95; 95% CI, 0.84 to 1.07; P=0.42) (Fig. 1A).

There was no significant heterogeneity in the effect of the trial regimen on the primary outcome in the six prespecified subgroups (Fig. 1B). A post hoc sensitivity analysis that excluded patients who had received open-label glucocorticoids did not alter the primary outcome result (odds ratio, 0.96; 95% CI, 0.82 to 1.12; P=0.59).

SECONDARY OUTCOMES

There was no significant between-group difference in mortality at 28 days (Table 2, and Table S10 in the Supplementary Appendix). The time to the resolution of shock was shorter in the hydrocortisone group than in the placebo group (median, 3 days [interquartile range, 2 to 5] vs. 4 days [interquartile range, 2 to 9]; hazard ratio, 1.32; 95% CI, 1.23 to 1.41; P<0.001) (Fig. 2, and Fig. S6A and S6B in the Supplementary Appendix).

The time to discharge from the ICU was shorter in the hydrocortisone group than in the placebo group (median, 10 days [interquartile range, 5 to 30] vs. 12 days [interquartile range, 6 to 42]; hazard ratio, 1.14; 95% CI, 1.06 to 1.23; P<0.001) (Fig. S6C and S6D in the Supplementary Appendix). After adjustment for multiple comparisons, there was no significant between-group difference in the number of days alive and out of the ICU (P=0.047; threshold level for significance after adjustment for multiple comparisons, P=0.005) (Table 2, and Table S11 in the Supplementary Appendix).

Patients in the hydrocortisone group had a shorter duration of the initial episode of mechanical ventilation than did those in the placebo group (median, 6 days [interquartile range, 3 to 18] vs. 7 days [interquartile range, 3 to 24]; hazard ratio, 1.13; 95% CI, 1.05 to 1.22; P<0.001), but taking into account episodes of recurrence of ventilation, there were no significant differences in the number of days alive and free from mechanical ventilation (Table 2, and Fig. S6G and S6H in the Supplementary Appendix).

There were no significant between-group differences with respect to the rate of recurrence of shock, the time to hospital discharge, the number of days alive and out of hospital, the rate of recurrence of mechanical ventilation, the duration and rate of use of renal-replacement therapy, and the rate of development of new-onset bacteremia or fungemia (Table 2, and Fig. S6E and S6F in the Supplementary Appendix).

Fewer patients in the hydrocortisone group than in the placebo group received a blood transfusion (37.0% vs. 41.7%; odds ratio, 0.82; 95% CI, 0.72 to 0.94; P=0.004). Among the patients who received a transfusion, there was no significant between-group difference with respect to the mean total volume of blood transfused (Fig. S7 in the Supplementary Appendix).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydrocortisone (N = 1853)	Placebo (N = 1860)
Age — yr	62.3±14.9	62.7±15.2
Male sex — no./total no. (%)	1119/1853 (60.4)	1140/1860 (61.3)
Weight — kg	85.8±26.6	85.6±26.3
Admission type — no./total no. (%)†		
Medical	1273/1849 (68.8)	1266/1857 (68.2)
Surgical	576/1849 (31.2)	591/1857 (31.8)
APACHE II score‡		
Median	24.0	23.0
Interquartile range	19.0–29.0	18.0–29.0
Therapy at baseline — no./total no. (%)§		
Mechanical ventilation	1845/1849 (99.8)	1855/1857 (99.9)
Inotropes or vasopressors	1843/1853 (99.5)	1854/1860 (99.7)
Norepinephrine	1823/1853 (98.4)	1821/1860 (97.9)
Vasopressin	280/1853 (15.1)	321/1860 (17.3)
Epinephrine	134/1853 (7.2)	113/1860 (6.1)
Other	157/1853 (8.5)	173/1860 (9.3)
Antimicrobial agent	1817/1848 (98.3)	1821/1857 (98.1)
Renal-replacement therapy	228/1849 (12.3)	242/1857 (13.0)
Physiological variables¶		
Heart rate — beats/min	96.0±21.6	95.0±20.9
Mean arterial pressure — mm Hg	72.5±8.2	72.2±8.3
Central venous pressure — mm Hg	12.0±5.2	12.1±5.3
Lowest mean arterial pressure — mm Hg	57.3±8.5	57.1±9.1
Highest lactate level — mg/dl	34.2±29.1	34.5±28.2
Highest bilirubin level — mg/dl	1.7±2.4	1.7±2.4
Highest creatinine level — mg/dl	2.2±2.0	2.1±1.7
Lowest Pao_2:FIo_2	164.6±91.3	166.4±91.9
Highest white-cell count — cells $\times 10^{-9}$/liter	17.4±11.4	17.8±14.7
Primary site of infection — no./total no. (%)		
Pulmonary	623/1844 (33.8)	677/1854 (36.5)
Abdominal	477/1844 (25.9)	467/1854 (25.2)
Blood	316/1844 (17.1)	325/1854 (17.5)
Skin or soft tissue	137/1844 (7.4)	116/1854 (6.3)
Urinary	146/1844 (7.9)	133/1854 (7.2)
Other	145/1844 (7.9)	136/1854 (7.3)
Time from ICU admission to randomization — hr	26.1±70.7	28.9±72.8
Time from shock onset to randomization — hr	20.9±91.9	21.2±83.4
According to subgroup — no./total no. (%)		
Catecholamine dose >15 μg/min	981/1834 (53.5)	1013/1832 (55.3)
Pulmonary sepsis	805/1853 (43.4)	840/1860 (45.2)

Table 1. (Continued.)

Characteristic	Hydrocortisone (N=1853)	Placebo (N=1860)
APACHE II score ≥25	847/1847 (45.9)	800/1856 (43.1)
Time from shock onset to randomization		
<6 hr	357/1842 (19.4)	349/1851 (18.9)
6 to <12 hr	516/1842 (28.0)	495/1851 (26.7)
12 to <18 hr	441/1842 (23.9)	427/1851 (23.1)
18 to 24 hr	528/1842 (28.7)	580/1851 (31.3)

* Plus–minus values are means ±SD. No significant differences between the groups were observed at baseline.
† Surgical admissions were defined as patients being admitted to the intensive care unit (ICU) from the operating room or the recovery room. All other admissions were considered to be medical admissions.
‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II are assessed on a scale from 0 to 71, with higher scores indicating a higher risk of death (a score of ≥25 has been used as a cutoff point to identify patients at a higher risk for death).[23-25]
§ The values for baseline therapies denote the value in the 24 hours before randomization. The percentages of patients who underwent mechanical ventilation or who received inotropic or vasopressor support was not 100% at baseline, which indicates the randomization of ineligible patients. Other inotropes or vasopressors include drugs such as dopamine, dobutamine, levosimendan, or metaraminol.
¶ The values for heart rate, the mean arterial pressure, and the central venous pressure represent the most recent values that were observed before randomization. The lowest values for the mean arterial pressure and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (the partial Pao_2:FIO_2) and the highest values for the lactate, bilirubin, and creatinine levels and the white-cell count were measured during the 24 hours before randomization. To convert the values for lactate to millimoles per liter, multiply by 0.11. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

ADVERSE EVENTS

A total of 33 adverse events was reported in the trial population, with a higher percentage in the hydrocortisone group than in the placebo group (1.1% vs. 0.3%, P=0.009). There were 6 serious adverse events, with 4 occurring in the hydrocortisone group and 2 in the placebo group (Table 3). The list of protocol violations and the results of the interim analyses are presented in Tables S12 and S13, respectively, in the Supplementary Appendix.

DISCUSSION

We found that the administration of hydrocortisone did not result in lower 90-day mortality than placebo among patients with septic shock. This effect did not differ in any of the six prespecified subgroups. We observed a more rapid resolution of shock and a lower incidence of blood transfusion among patients who received hydrocortisone than among those who received placebo. Patients who had been assigned to receive hydrocortisone had a shorter time to ICU discharge and earlier cessation of the initial episode of mechanical ventilation than did those who had been assigned to receive placebo. There were no significant between-group differences with respect to mortality at 28 days, the rate of recurrence of shock, the number of days alive and out of the ICU or hospital, the duration and rate of recurrence of mechanical ventilation, the rate of use of renal-replacement therapy, or the rate of new-onset bacteremia or fungemia. Patients who had been assigned to receive hydrocortisone had more adverse events than did those who had been assigned to receive placebo, but these events did not affect patient-centered outcomes.

Our pragmatic trial was designed with statistical power to detect a clinically plausible effect on mortality. To reduce bias, we used a central randomization process and ensured the concealment and blinding of trial-group assignments, which were independently verified. We published our statistical analysis plan before unblinding.

We chose 90-day mortality as a patient-centered primary outcome and specifically targeted a population of patients who had high requirements for vital organ support (use of mechanical ventilation and ≥4 hours of vasopressor therapy

Table 2. Outcomes.*

Outcome	Hydrocortisone (N=1853)	Placebo (N=1860)	Odds Ratio, Hazard Ratio, or Absolute Difference (95% CI)	P Value
Primary outcome				
90-day mortality — no./total no. (%)	511/1832 (27.9)	526/1826 (28.8)	0.95 (0.82 to 1.10)†	0.50
Secondary outcomes				
28-day mortality — no./total no. (%)	410/1841 (22.3)	448/1840 (24.3)	0.89 (0.76 to 1.03)†	0.13
Median time to resolution of shock (IQR) — days	3 (2 to 5)	4 (2 to 9)	1.32 (1.23 to 1.41)‡	<0.001
Recurrence of shock — no. (%)	365 (19.7)	343 (18.4)	1.07 (0.94 to 1.22)†	0.32
Median time to discharge from the ICU (IQR) — days	10 (5 to 30)	12 (6 to 42)	1.14 (1.06 to 1.23)‡	<0.001
No. of days alive and out of the ICU	58.2±34.8	56.0±35.4	2.26 (0.04 to 4.49)§	0.047¶
Median time to discharge from the hospital (IQR) — days	39 (19 to NA)	43 (19 to NA)	1.06 (0.98 to 1.15)‡	0.13
No. of days alive and out of the hospital	40.0±32.0	38.6±32.4	1.45 (−0.59 to 3.49)§	0.16
Median time to cessation of initial mechanical ventilation (IQR) — days	6 (3 to 18)	7 (3 to 24)	1.13 (1.05 to 1.22)‡	<0.001
No. of days alive and free from mechanical ventilation	61.2±35.6	59.1±36.1	2.18 (−0.11 to 4.46)§	0.06
Recurrence of mechanical ventilation — no./total no. (%)	180/1842 (9.8)	154/1850 (8.3)	1.18 (0.96 to 1.45)†	0.11
No. of days alive and free from renal-replacement therapy	42.6±39.1	40.4±38.5	2.37 (−2.00 to 6.75)§	0.29
Use of renal-replacement therapy — no. (%)	567 (30.6)	609 (32.7)	0.94 (0.86 to 1.03)†	0.18
New-onset bacteremia or fungemia — no. (%)	262 (14.1)	262 (14.1)	1.00 (0.86 to 1.16)†	0.96
Blood transfusion — no./total no. (%)	683/1848 (37.0)	773/1855 (41.7)	0.82 (0.72 to 0.94)†	0.004

* Plus–minus values are means ±SD. Medians with interquartile ranges (IQR) are presented for not normally distributed variables. The analyses of mortality at day 90 and day 28 that are reported in this table, with adjustment for stratification variables, were performed with the use of logistic regression, with the inclusion of trial group and admission type as fixed effects and trial site as a random effect. Unadjusted mortality is reported in Table S10 in the Supplementary Appendix. The notation NA (not available) in the IQR for the time to hospital discharge indicates that less than 75% of the patients (the upper limit of the IQR) had been discharged from the hospital by day 90, so the data are not reported. Adjustments for multiple comparisons for all secondary outcomes are reported in Table S11 in the Supplementary Appendix. Informed consent could be obtained for the use of all or part of the data (Fig. S1 in the Supplementary Appendix). Consequently, the numbers of patients for whom data are available for the analyses varies.

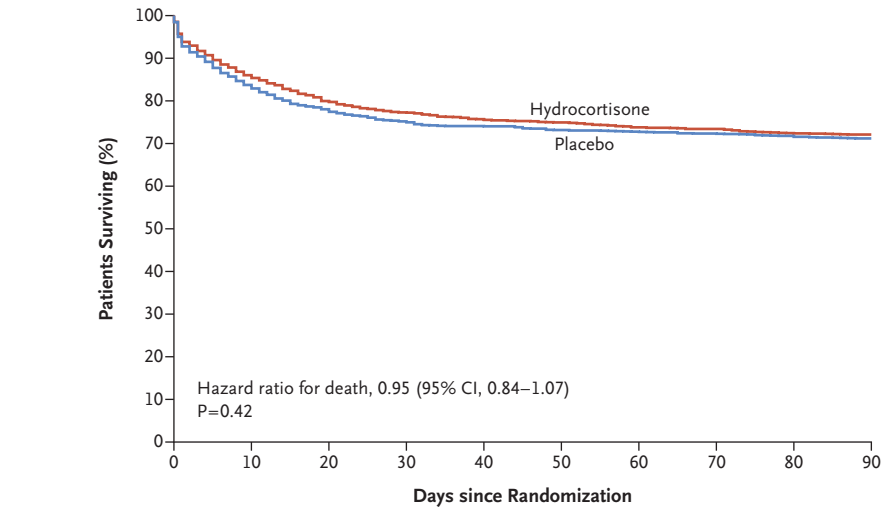
† This value is an odds ratio.

‡ This value is a hazard ratio.

§ This value is the mean absolute difference between groups.

¶ The results for this secondary outcome were not significant after adjustment for multiple comparisons (threshold level, P=0.005).

A Survival



No. at Risk

Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

B Subgroup Analysis of Death at 90 Days

Subgroup	Hydrocortisone	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Sex				0.53
Male	312/1106 (28.2)	336/1122 (29.9)	0.92 (0.76–1.10)	
Female	199/726 (27.4)	190/704 (27.0)	1.01 (0.80–1.28)	
Admission type				0.73
Surgical	125/568 (22.0)	138/580 (23.8)	0.91 (0.69–1.21)	
Medical	386/1264 (30.5)	388/1245 (31.2)	0.97 (0.81–1.15)	
Catecholamine dose				0.25
≤15 μg/min	224/968 (23.1)	228/995 (22.9)	1.02 (0.82–1.26)	
>15 μg/min	281/849 (33.1)	291/805 (36.1)	0.86 (0.70–1.05)	
Site of sepsis				0.63
Pulmonary	243/799 (30.4)	250/828 (30.2)	0.99 (0.80–1.23)	
Other	268/1033 (25.9)	276/998 (27.7)	0.92 (0.76–1.12)	
APACHE II score				0.17
≥25	326/840 (38.8)	297/785 (37.8)	1.01 (0.83–1.24)	
<25	184/990 (18.6)	229/1039 (22.0)	0.82 (0.66–1.02)	
Time from shock onset to randomization				0.08
<6 hr	110/352 (31.2)	96/344 (27.9)	1.16 (0.83–1.61)	
6 to <12 hr	127/511 (24.9)	153/486 (31.5)	0.71 (0.54–0.94)	
12 to <18 hr	119/437 (27.2)	106/423 (25.1)	1.13 (0.83–1.54)	
≥18 hr	154/525 (29.3)	167/566 (29.5)	0.99 (0.76–1.29)	

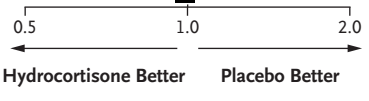


Figure 1. Rate of Survival and the Risk of Death at 90 Days, According to Subgroup.

Panel A shows Kaplan–Meier estimates of the survival rate among patients receiving hydrocortisone or placebo. The P value was calculated with the use of a Cox proportional-hazards model that included the randomized trial group, admission type (medical or surgical), and a random effect of trial center. Panel B shows the odds ratio of death at 90 days in the six prespecified subgroups. The size of the square representing the odds ratio reflects the relative numbers in each subgroup, and horizontal bars represent 95% confidence intervals. P values are for heterogeneity of the effect of the trial regimen on the primary outcome in each subgroup. Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II are assessed on a scale from 0 to 71, with higher scores indicating a higher risk of death (a score of ≥25 has been used as a cutoff point to identify patients at a higher risk for death).[23-25] Data on admission type were missing for 1 patient in the placebo group; on the catecholamine dose for 15 in the hydrocortisone group and for 26 in the placebo group; on the APACHE II score for 2 and 2, respectively; and on the time from shock onset to randomization for 7 and 7, respectively.

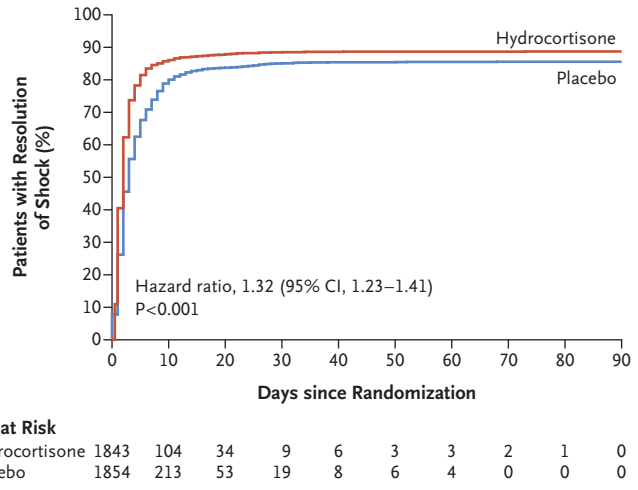


Figure 2. Cumulative Incidence Function of Time from Randomization to Resolution of Shock.

The cumulative incidence function plot was created by treating death as a competing risk.

Table 3. Adverse Events.*

Adverse Event	Hydrocortisone (N=1835)	Placebo (N=1829)
No. of patients with event	21	6
No. of events		
Total adverse events	27	6
Hyperglycemia	6	3
Hypernatremia	3	0
Hyperchloremia	1	0
Hypertension	3	0
Bleeding	2	1†
Encephalopathy	3	0
Leukocytosis	2	0
Myopathy‡	3†	0
Septic arthritis	1	0
Ischemic bowel	1†	0
Abdominal-wound dehiscence	0	1†
Circulatory shock	1†	0
Thrombocytopenia	1	0
Miscellaneous	0	1

* The determination that an adverse event, serious adverse event, or suspected unexpected serious adverse reaction (SUSAR) had occurred was at the discretion of the treating clinician. Prospective definitions of adverse events, serious adverse events, and SUSARs and a system of reporting are provided in section 11 of the protocol. An adverse event was any adverse reaction that was thought to be related to the trial regimen and listed in the product information sheet. A serious adverse event was defined as any adverse reaction that resulted in death, was life-threatening, resulted in the prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity. A SUSAR was defined as a serious adverse event whose nature, severity, specificity, or outcome was not consistent with the terms or descriptions used in the product information sheet. Some patients had more than one event. No SUSARS were reported during the trial.

† A serious adverse event was reported. There were a total of four serious adverse events (two of myopathy, one of ischemic bowel, and one of circulatory shock) in the hydrocortisone group and two events (one of bleeding and one of abdominal-wound dehiscence) in the placebo group.

‡ Myopathy was reported on the basis of clinical findings of muscle weakness or biochemical evidence of an increased creatine kinase level.

before randomization) and a substantial risk of death. The trial was successful in enrolling the intended population.

A high proportion of eligible patients received the trial intervention as planned, and few enrolled patients were lost to follow-up. The ratio of patients who underwent randomization to those who were eligible for inclusion was high: 0.69:1, a ratio that approaches that seen in other large-scale trials.[29] The inclusion of 69 sites in five countries increases the external validity of the results.

Our trial differs from previously published trials in several respects.[10,11] We administered hydrocortisone by means of continuous infusion, because such a plan has been shown to attenuate the inflammatory response and reverse shock.[30] Practice guidelines for septic shock suggest that infusions may minimize potentially harmful metabolic effects of glucocorticoids.[15,31] A tapering strategy was not used for the discontinuation of glucocorticoids, because a beneficial effect of these agents on survival was previously reported without tapering.[10] A recent study that compared abrupt cessation with a tapering strategy showed no benefits from tapering.[32] We did not perform corticotropin testing, because its interpretation in critically ill patients is controversial[33-35] and such testing is not recommended in current clinical practice guidelines.[15] We excluded patients who had received etomidate before randomization. We did not administer fludrocortisone, because it has been shown previously to be ineffective.[36]

Our trial had limitations. Within the context

of a large pragmatic trial, we collected data on only adverse events that had been judged by the treating clinicians to be related to the trial regimen, and we did not adjudicate this judgment. This approach may weaken the inferences about adverse events. We did not collect data regarding all possible secondary infections, and we recorded only bacteremia and fungemia, which are less subject to diagnostic error or ascertainment bias. We did not adjudicate the appropriateness of antibiotic therapy. We used rates of recurrence of ventilation as a surrogate for myopathy but did not assess long-term neuromuscular weakness.

Our trial provides evidence about the role of hydrocortisone as an adjunctive treatment in patients with septic shock. Although we did not observe a significant difference between the hydrocortisone group and the placebo group with regard to 90-day mortality, some secondary outcomes were better in the group that received the active treatment. Our observation of the hemodynamic effects of hydrocortisone is consistent with those in previous studies.[37-39] These hemodynamic effects may represent a beneficial role of hydrocortisone. There was a lower incidence of transfusion in the hydrocortisone group than in the placebo group, a finding that may be regarded as hypothesis-generating. A detailed cost–benefit assessment of these results was not done, but such an analysis may inform clinicians about the overall cost-effectiveness of hydrocortisone in patients with septic shock.

In conclusion, in patients with septic shock who were undergoing mechanical ventilation, the administration of a continuous infusion of hydrocortisone did not result in lower mortality at 90 days than placebo.

Supported by project grants from the National Health and Medical Research Council of Australia (grant nos., 1004108 and 1124926) and the Health Research Council of New Zealand (grant no., 12/306), by indirect funding from the National Institute of Health Research in the United Kingdom, and by Practitioner Fellowships from the National Health and Medical Research Council of Australia (to Drs. Finfer, Bellomo, and Myburgh).

Dr. Perner reports receiving grant support from CSL Behring, Ferring Pharmaceuticals, and Fresenius Kabi; and Dr. Rhodes, serving as co-chair of the Surviving Sepsis Campaign. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients and their families for their participation in this trial and the intensive care unit clinical and research staff at all the participating sites.

APPENDIX

The authors' full names and academic degrees are as follows: Balasubramanian Venkatesh, M.D., Simon Finfer, M.D., Jeremy Cohen, M.D., Ph.D., Dorrilyn Rajbhandari, R.N., Yaseen Arabi, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., M.Res., Maryam Correa, Ph.D., Parisa Glass, Ph.D., Meg Harward, R.N., Christopher Joyce, M.D., Ph.D., Qiang Li, M.Sc., Colin McArthur, M.D., Anders Perner, M.D., Ph.D., Andrew Rhodes, M.D., Kelly Thompson, R.N., M.P.H., Steve Webb, M.D., Ph.D., and John Myburgh, M.D., Ph.D.

The authors' affiliations are as follows: the George Institute for Global Health, University of New South Wales (B.V., S.F., D.R., L.B., M.C., P.G., M.H., Q.L., K.T., J.M.), St. George Clinical School, St. George Hospital (J.M.), Sydney Medical School, University of Sydney (B.V., S.F., J.M.), and Royal North Shore Hospital (S.F.), Sydney, the Princess Alexandra Hospital (B.V., C.J.) and Royal Brisbane and Women's Hospital (J.C.), University of Queensland, and the Wesley Hospital (B.V., J.C.), Brisbane, Austin Hospital (R.B.), the School of Medicine, University of Melbourne (R.B.), and the Australian and New Zealand Research Centre (R.B.), School of Public Health and Preventive Medicine (R.B., S.W., J.M.), Monash University, Melbourne, VIC, and Royal Perth Hospital (S.W.) and the School of Medicine and Pharmacology, University of Western Australia (S.W.), Perth — all in Australia; King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia (Y.A.); the Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand (C.M.); Rigshospitalet, University of Copenhagen, Copenhagen (A.P.); and St. George's University Hospitals NHS Foundation Trust, St. George's University of London, London (A.R.).

REFERENCES

1. Reinhart K, Daniels R, Kissoon N, Machado FR, Schachter RD, Finfer S. Recognizing sepsis as a global health priority — a WHO resolution. N Engl J Med 2017; 377:414-7.
2. Fleischmann C, Scherag A, Adhikari NK, et al. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med 2016;193:259-72.
3. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014; 312:90-2.
4. Machado FR, Cavalcanti AB, Bozza FA, et al. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD): an observational study. Lancet Infect Dis 2017;17:1180-9.
5. Rhee C, Dantes R, Epstein L, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009-2014. JAMA 2017;318:1241-9.
6. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 2004;30:589-96.
7. Schumer W. Steroids in the treatment of clinical septic shock. Ann Surg 1976; 184:333-41.
8. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. N Engl J Med 1984;311:1137-43.
9. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317:653-8.
10. Annane D, Sébille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862-71.

11. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111-24.
12. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA 2009;301:2362-75.
13. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. Cochrane Database Syst Rev 2015;12:CD002243.
14. Volbeda M, Wetterslev J, Gluud C, Zijlstra JG, van der Horst IC, Keus F. Glucocorticosteroids for sepsis: systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2015;41:1220-34.
15. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304-77.
16. Beale R, Janes JM, Brunkhorst FM, et al. Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry. Crit Care 2010;14:R102.
17. Venkatesh B, Myburgh J, Finfer S, et al. The ADRENAL study protocol: adjunctive corticosteroid treatment in critically ill patients with septic shock. Crit Care Resusc 2013;15:83-8.
18. Billot L, Venkatesh B, Myburgh J, et al. Statistical analysis plan for the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial. Crit Care Resusc 2017;19:183-91.
19. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992;101:1644-55.
20. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1984;310:1415-21.
21. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
22. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J. A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med 2008;34:2226-34.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.
24. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 2005;353:1332-41.
25. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 2012;366:2055-64.
26. Ripatti S, Palmgren J. Estimation of multivariate frailty models using penalized partial likelihood. Biometrics 2000;56:1016-22.
27. Brock GN, Barnes C, Ramirez JA, Myers J. How to handle mortality when investigating length of hospital stay and time to clinical stability. BMC Med Res Methodol 2011;11:144.
28. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65-70.
29. Cooper DJ, McQuilten ZK, Nichol A, et al. Age of red cells for transfusion and outcomes in critically ill adults. N Engl J Med 2017;377:1858-67.
30. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med 2003;167:512-20.
31. Loisa P, Parviainen I, Tenhunen J, Hovilehto S, Ruokonen E. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. Crit Care 2007;11:R21.
32. Ibarra-Estrada MA, Chávez-Peña Q, Reynoso-Estrella CI, et al. Timing, method and discontinuation of hydrocortisone administration for septic shock patients. World J Crit Care Med 2017;6:65-73.
33. Venkatesh B, Mortimer RH, Couchman B, Hall J. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. Anaesth Intensive Care 2005;33:201-9.
34. Briegel J, Sprung CL, Annane D, et al. Multicenter comparison of cortisol as measured by different methods in samples of patients with septic shock. Intensive Care Med 2009;35:2151-6.
35. Venkatesh B, Cohen J. The utility of the corticotropin test to diagnose adrenal insufficiency in critical illness: an update. Clin Endocrinol (Oxf) 2015;83:289-97.
36. Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 2010;303:341-8.
37. Annane D. Glucocorticoids in the treatment of severe sepsis and septic shock. Curr Opin Crit Care 2005;11:449-53.
38. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 1995;332:1351-62.
39. Shi LJ, He HY, Liu LA, Wang CA. Rapid nongenomic effect of corticosterone on neuronal nicotinic acetylcholine receptor in PC12 cells. Arch Biochem Biophys 2001;394:145-50.