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The CORTICUS randomized, double-blind, placebo-controlled study of hydrocortisone therapy in patients with septic shock

Short title: CORTICUS study of hydrocortisone therapy in patients with septic shock

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Abstract

BACKGROUND. Hydrocortisone treatment is widely used in septic shock though survival benefit has only been reported in patients remaining hypotensive after fluid and vasopressor resuscitation whose plasma cortisol fails to rise appropriately to corticotropin. This study assessed outcome effects of hydrocortisone in a general septic shock population.

METHODS. Multicenter, randomized, double-blind, placebo-controlled trial of 50 mg intravenous hydrocortisone (or placebo) every 6 hours for 5 days, then tapered off over six days. The primary outcome was 28-day mortality in corticotropin nonresponders.

RESULTS. Five hundred patients were recruited of whom 499 (251 hydrocortisone, 248 placebo) were analyzable. Of these, 233 (46.7%) were corticotropin nonresponders (125 hydrocortisone, 108 placebo). No difference in 28-day mortality was seen in nonresponders (39.2% hydrocortisone, 36.1% placebo; p=0.69), or responders (28.8% hydrocortisone, 28.7% placebo; p=1.00). Overall, 86/251 (34.3%) hydrocortisone and 78/248 (31.5%) placebo patients died by 28 days (p=0.51). Hydrocortisone hastened the time to shock reversal in nonresponders (p =0.056), responders (p=0.0001) and all patients (p=0.0004). However, it failed to increase the proportion of patients with shock

reversal in the total population or either corticotropin subset. There were more episodes of superinfection including new sepsis or septic shock in the hydrocortisone group. Only 500 rather than the projected 800 patients were enrolled because of slow recruitment, termination of funding and time expiry of the trial drug.

CONCLUSIONS. Hydrocortisone failed to improve survival or shock reversal in a general septic shock population, either overall or in corticotropin-nonresponders, though it did hasten shock recovery. (ClinicalTrials.gov number, NCT00147004).

Abstract word count- 250

Severe sepsis is a major worldwide cause of mortality and morbidity [1,2] Septic shock, the most severe manifestation, occurs in 2-20% of inpatients.[3] Its incidence is rising [4] and a mortality of 33-61% is reported in the placebo group of recent multicenter trials. [5,6,7,8]

The use of corticosteroids as an adjunctive therapy has been controversial for decades. [9] After the Schumer study,[10] high-dose, short-course glucocorticoids became accepted therapy. Subsequent studies, however, failed to confirm survival benefit with this regimen and suggested an increase in superinfection-related mortality.[11-13] Recent studies using lower doses (200-300 mg per day) of hydrocortisone for longer durations reported earlier reversal of shock [14-18] and improved survival. [14,16] This was particularly apparent in nonresponders to corticotropin, the prognostic importance of which had been previously recognized in critical illness.[19,20] Recent meta-analyses [21,22] , reviews [20] and guidelines [23] have advocated the use of 'low-dose' hydrocortisone in septic shock. These recommendations were primarily based on a study of septic shock patients remaining hypotensive after at least one hour of resuscitation with fluids and vasopressors,[16] in which survival benefit was seen in corticotropin nonresponders receiving hydrocortisone and fludrocortisone. The CORTICUS study evaluated the efficacy and safety of low-dose

hydrocortisone therapy in a broader septic shock population, in particular patients responding to corticotropin in whom benefit was unproven. [9]

Methods

Experimental design and study organization

This was a multicenter, randomized, double-blind, placebo-controlled study. The protocol was approved by the Ethics Committees of the 52 participating intensive care units (ICUs). Patients were enrolled from March 2002 until November 30, 2005. An Independent Data Safety and Monitoring Board (DSMB) met after each of three interim analyses. At study end, a Clinical Evaluation Committee blindly assessed the appropriateness of anti-infective treatments.

Patients

Patients of 18 years of age or above and hospitalized in participating ICUs were prospectively enrolled in the study if they met all eligibility criteria (Supplementary Appendix Table 1). Inclusion criteria included: (1) Clinical evidence of infection, (2) Evidence of a systemic response to infection, (3) Evidence of shock within the previous 72 hours defined by a systolic blood pressure (SBP) <90 mmHg despite adequate fluid replacement OR need for vasopressors for at least one hour, and hypoperfusion or organ

dysfunction attributable to sepsis, and (4) Informed consent according to local regulations. Notable exclusion criteria included underlying disease with a poor prognosis, moribund patients likely to die within 24 hours, immunosuppression and prior administration of corticosteroids.

Randomization

Randomization (1:1) was stratified by center in blocks of four using a computer random number generator list provided by a statistician not involved in eligibility determinations, treatment administration or outcome assessments. In each center, study medication (hydrocortisone or placebo) sealed in sequentially numbered identical boxes contained the entire treatment for each patient to be administered sequentially. The sequence was concealed to investigators. All patients, medical and nursing staffs, pharmacists, investigators and members of the DSMB remained blinded throughout the study period.

Treatments

Hydrocortisone was prepared (Rotexmedica, Trittau, Germany) in vials containing 100 mg of hydrocortisone hemisuccinate powder with ampoules containing 2 ml of sterile water diluent and then coded and blinded centrally (Klocke Verpackungs-Service GmbH, Weingarten, Germany). Placebo was indiscernible from active treatment. Study drug was administered as a 50 mg intravenous bolus every six hours for 5 days, then tapered to 50 mg intravenously every 12 hours for days 6-8, 50 mg every 24 hours for days 9-11 and then stopped. A total of 29 doses were given. Evidence-based guidelines for patient management were encouraged. [24]

Definitions

Organ system failure was defined for each of the 6 major organ systems as a Sequential Organ Failure Assessment (SOFA) score of 3 or 4 points. [25] Reversal of shock was defined as the maintenance of a SBP ≥90 mmHg without vasopressor support for ≥24 hours. Superinfection was defined as a new infection occurring ≥48 hours after study medication commenced. [26] New sepsis was defined as a new septic episode with or without microbiological confirmation. New septic shock was defined as a new septic shock

episode after reversal of the initial septic shock. Nonresponders to the corticotropin test were defined by a cortisol increase ≤9 μg/dl (248 nmol/l). [16]

Data collection at inclusion

Clinical evaluation. The following data were recorded: 1) general characteristics including demographics, diagnoses and recent surgery, 2) severity of illness assessed by vital signs, Simplified Acute Physiology Score (SAPS) II, [27] and SOFA score, [25] and 3) interventions including type and doses of vasopressors, antibiotics and adjunctive treatment such as corticosteroids and etomidate.

Laboratory variables. Hematological and chemistry data, blood gas determinations, and cultures of blood and other specimens drawn from potential sites of infection were recorded. A short corticotropin test was performed using blood samples taken immediately before and 60 minutes after an intravenous bolus of 0.25 mg tetracosactrin (Novartis, Nuremberg, Germany or Alliance, Chippenham, UK). After centrifugation, serum samples were stored at -20℃ or below until assayed. To reduce heterogeneity in cortisol determination, all samples were measured blindly and serially before interim and final

analyses in a central laboratory using the ELECSYS Cortisol assay® (Roche Diagnostics, Mannheim/Penzberg, Germany).

Follow-up

During the 28-day period post-randomization, data were collected for vital signs, results from laboratory tests and cultures of specimens drawn from any new site of infection and any major interventions performed. Mortality at 28 days, discharge from ICU, hospital and at one year after randomization were recorded.

Endpoints

The primary endpoint was 28-day mortality in nonresponders to the corticotropin test. Secondary endpoints determined *a priori* were (i) 28-day mortality in responders to corticotropin and in all patients, (ii) ICU, hospital and one-year mortality, (iii) organ system failure reversal including shock, and (iv) ICU and hospital stay.

Safety was assessed by recording adverse events particularly superinfection, gastrointestinal bleeding, hyperglycemia, hypernatremia, clinical muscular weakness, stroke, acute myocardial infarction and peripheral ischemia.

Methods to enhance quality of measurements included biannual investigator meetings, newsletters and random quality assurance evaluations.

Statistical methods

A sample size of 800 (400 patients per group) was needed to achieve 80% statistical power to detect an absolute decrease in mortality of 10% from an existing mortality rate of 50% in the corticotropin nonresponder group (40% in the total group).

All analyses were performed according to a pre-established plan. The population was analyzed by an “intention to treat” principle. Twenty-eight day all-cause mortality was analyzed by the Fisher’s exact test for differences between treatment groups. A maximum overall two-sided probability of a type-I error of 5% was accepted. The test result was corrected for two interim analyses for efficacy. Splitting the alpha error function was performed according to the method of O'Brian and Flemming (p=0.0006, p=0.005 and

p=0.047 for the first, second and final analysis, respectively). Twenty-eight day mortality was significantly different if the stopping criteria of the interim analysis were met or the two-sided p value of the final analysis was <0.047. All other secondary efficacy variables were assumed to be significantly different for p-values <0.05. Cumulative survival Kaplan-Meier curves during the 28-day observation period were constructed and compared using the log-rank test. Median time to reversal of septic shock was calculated by Kaplan-Meier analysis. Adverse events were reported for the per protocol population. Multivariate analyses of the 28-day mortality were carried out by logistic regression models.

Results

Study patients

Five hundred patients were enrolled (Figure 1). One patient in the hydrocortisone group was excluded because consent was withdrawn. Of the remaining 499 patients, all patients met entry criteria though 15 fulfilled exclusion criteria (8 hydrocortisone, 7 placebo patients) as 14 had received previous steroids and one had undergone prior CPR. Eighty-seven percent of both placebo and active groups received ≥90% of study drug.

There were 233 (46.7%) corticotropin nonresponders (hydrocortisone 125; placebo 108) and 254 (50.9%) responders (hydrocortisone 118; placebo 136). Results were unknown in 12 (2.4%) patients (hydrocortisone 8; placebo 4). Etomidate was used in 51 (20%) hydrocortisone and 45 (18%) placebo patients before study entry, and in 22 (9%) and 20 (8%) after study enrollment. More of the patients receiving etomidate were nonresponders [58/96 (60%) versus 175/403 (43%)]. The median time between the last dose of etomidate and enrollment was 14 (range:1-67) hours.

At baseline, the two groups were well balanced for demographics (Table 1), clinical characteristics (Table 2), and the type and site of infection and infecting organisms (Supplementary Appendix Table 2).

Main Outcomes

Mortality

The primary outcome of 28-day mortality in corticotropin nonresponders revealed no difference between the hydrocortisone [49 deaths (39.2%; 95% CI: 30.5-47.9%)] and placebo [39 deaths (36.1%; 95% CI: 26.9-45.3%)] groups. Likewise, no difference was seen in 28-day mortality in corticotropin responders with 34 (28.8%; 95% CI: 20.6-37.0%) and 39 (28.7%; 95% CI:21.1-36.3%) deaths in the hydrocortisone and placebo groups, respectively. Overall, there were 86 deaths (34.3%; 95% CI: 28.3-40.2%) in the hydrocortisone group and 78 deaths (31.5%; 95% CI: 25.6-37.3%) in the placebo group.

No mortality differences were seen between groups (or in responder/nonresponder subsets) at any other time point. Kaplan Meier survival curves are shown in Figures 2a-c and odds ratio and 95% confidence intervals in Table 3. *Post hoc* analysis showed a mortality rate of 31/69 (45%) in steroid-treated patients vs. 32/57 (56%) in placebo

patients (difference –11% (95% CI: -18.6 to 6.2%), p=0.28) with SBP persisting <90 mmHg within 30 hours of study entry, and 55/181 (30%) in steroid-treated vs. 46/189 (24%) in placebo patients (difference 6% (95%CI: -3.0 to 15.1%), p=0.20) with SBP ≥90 mmHg within 30 hours of study entry. *Post hoc* analysis of the 198 patients receiving study drug within 12 hours from baseline, demonstrated a similar mortality rate of 71/198 (36%) in steroid-treated patients vs. 57/186 (31%) in placebo patients.

A post-hoc analysis revealed a trend to increased mortality in patients who received etomidate pre-randomization in both groups [23/51 (45%) hydrocortisone vs. 18/45 (40%) placebo] vs. not receiving etomidate [63/200 (32%) hydrocortisone vs. 60/203 (30%) placebo]. A logistic regression model adjusting for the treatment group (steroid/placebo), response to corticotropin (responder/non-responder), cortisol-baseline value (as continuous variable) and SAPS II Score revealed a p-value of 0.053 for the effect of etomidate.

Reversal of shock

The proportion of shock reversal was similar for nonresponders [95/125 (76.0%; 95% CI: 68.5-83.5%) hydrocortisone, 76/108 (70.4%; 95% CI: 61.8-79.0%) placebo, p = 0.41]; responders [100/118 (84.7%; 95% CI: 78.3-91.2%) hydrocortisone, 104/136 (76.5%; 95% CI: 69.3-83.6%) placebo, p = 0.13]; or all patients [200/251 (79.7%; 95% CI: 74.7-84.7%) hydrocortisone, 184/248 (74.2%; 95% CI: 68.7-79.6%) placebo, p = 0.18]. Differences in shock reversal between hydrocortisone and placebo groups with relative risks (95% CI) for nonresponders, responders and all patients respectively, were 5.6% -5.8-17.0%) and 1.08 (0.92-1.26), 8.3% -1.4-17.9%) and 1.11 (0.98-1.25), 5.5% (-1.9-12.9%) and 1.07 (0.98-1.18) in favor of hydrocortisone.Time to shock reversal was significantly shorter in patients receiving hydrocortisone, for the overall group (p=0.0004), responders (p=0.0001) and nonresponders (p=0.0.056) (Figures 3a-c). The median time (95% CI) to shock reversal was shorter in the hydrocortisone group: for all patients 3.3 days (2.9-3.9) vs. 5.8 days (5.2-6.9); responders 2.8 days (2.1-3.3) vs. 5.8 days (5.2-6.9); and nonresponders 3. 9 days (3.0-5.2) vs. 6.0 days (4.9-9.0).

The number of extubated patients on day 28 was similar in the hydrocortisone and placebo groups, [119 (52%) vs. 113 (53%), respectively]. For the 357 patients with cultured pathogens for their primary infection, the Clinical Evaluation Committee's

determined appropriate antimicrobial therapy for 126 of 173 (73%) steroid and 145 of 184 (79%) placebo treated patients. There was no difference between treatment groups nor outcome differences between patients receiving appropriate or inappropriate antibiotic therapy.

Steroid and other drug use

Eleven patients (4%) in the hydrocortisone group and 10 (4%) in the placebo group received steroids after study enrollment for allergic reactions, laryngeal edema, bronchospasm, brain edema, steroid replacement for chronic steroid therapy unknown at enrollment, acute respiratory distress syndrome and septic shock. Five patients received steroids for septic shock after completion of the study drug course. The number of patients receiving activated protein C and antithrombin III was not different in the two groups (Table 2).

Adverse events

There was an increased incidence of superinfections including new episodes of sepsis or septic shock [odds ratios (95% CI) of 1.37 (1.05-1.79)], hyperglycemia and

hypernatremia in the hydrocortisone group (Table 4). Neuromuscular weakness was rarely reported.

Discussion

This study found no impact of 'low-dose' hydrocortisone on 28-day mortality in septic shock patients, regardless of their adrenal responsiveness to corticotropin. Hydrocortisone did not significantly affect overall shock reversal but it did hasten the time to shock reversal.

These results are in marked contrast to the Annane study [16] where improved survival and shock reversal were reported in corticotropin nonresponders receiving hydrocortisone plus fludrocortisone. Differences may relate to (i) dissimilar patient populations - the Annane patients had higher SAPS II scores at baseline, an entry requirement of SBP <90 mmHg for >1 hour despite fluid and vasopressor therapy, and a much higher 28-day mortality in the placebo group (61% vs. 32% in CORTICUS); (ii) enrollment was only allowed within 8 hours of fulfilling entry criteria rather than the 72 hour window in CORTICUS; and (iii) fludrocortisone was not given in CORTICUS as 200mg hydrocortisone should provide adequate mineralocorticoid activity.[28] Furthermore, absorption of oral fludrocortisone is variable in the shock state. Although an analysis of patients with SBP persisting <90 mmHg at day 1 after fluid and vasopressor resuscitation showed a placebo mortality of 56% and an absolute reduction in mortality of 11% in the

hydrocortisone group, similar to that reported by Annane, [16] the subsets receiving study drug within 12 hours from baseline did not demonstrate any outcome differences.

As reported previously, [14,15,18] a decrease in time to shock reversal with hydrocortisone was found in this study. However, the total number of patients achieving shock reversal was unaffected. It remains unclear why vascular tone improves in some patients but not others. Unexpectedly, earlier shock reversal was greater in corticotropin responders but was not associated either with survival benefit or reduction in duration of ICU or hospital stay. These findings may be unrelated to adrenal insufficiency but could instead result from a direct interaction with mechanisms producing vascular hyporeactivity. [29,30] Alternatively, the effect may be due to a more widespread anti-inflammatory action of glucocorticoids, inhibiting expression of pro-inflammatory cytokines, mediators and receptors. [31]

The duration of steroid dosage may be pertinent, with any gain achieved by earlier shock reversal counterbalanced by later complications.[9] Annane stopped corticosteroid treatment abruptly after 7 days whereas, in CORTICUS, therapy was tapered from day 5 to day 11. Tapering was used because of the increase in pro-inflammatory mediators and hemodynamic deterioration after abrupt cessation of steroids. [17] The present study found

an increased incidence of superinfections including new episodes of sepsis or septic shock in the hydrocortisone group. Previous studies with high dose steroids have shown similar findings.[11] Interestingly, the ARDSnet study using higher dose steroids [32] and meta-analyses of studies with low doses [21,22] did not report higher rates of infectious complications.

Studies in the critically ill have reported an association between steroid therapy and the incidence of neuromuscular weakness**.** [32,33] This was not seen in CORTICUS although electrophysiological testing was not performed. The duration of mechanical ventilation was, however, similar in the two groups. Finally, the increased glucose levels in the hydrocortisone group may have contributed to an increased mortality. [34]

The use of etomidate for induction of anesthesia was similar to the Annane study[16] (24% vs. 23% in CORTICUS). Etomidate has a low cardiovascular complication profile [35] but a single dose can inhibit steroid metabolism for at least 24 hours in the critically ill. [36] An association between etomidate and the likelihood of adrenal hyporesponsiveness was also found in this study.

The prognostic importance of adrenal insufficiency in septic shock is well described.[19] Routine testing of adrenal function has been advocated to guide steroid

therapy. [16,18-21] In the present study a modest increase in 28-day mortality was seen in corticotropin nonresponders (38% vs 29% in responders) but there was no outcome difference with hydrocortisone treatment in either subset. The short corticotropin test does not appear useful for determining steroid treatment in septic shock and the results question the definition of relative adrenal insufficiency. Indeed, significant variability in cortisol levels has been described depending on the measurement methodology used. [37] Recent studies have described the poor relationship between total and free cortisol levels [38] and other issues concerning the dose, timing and type of corticotropin. [39]

Strengths of the present study include the fact that it was a European-wide, investigator-initiated study including 52 ICUs from 9 countries. Practically all the CONSORT requirements for reporting randomized trials were met a central laboratory was used for measuring cortisol and quality assurance evaluations revealed few problems. Limitations of the study include the lack of adequate power as only 500 patients were enrolled rather than the projected 800. This was due to a combination of slow recruitment likely related to a loss of equipoise in view of the various guidelines recommending steroid use, [23] termination of funding, and time expiry of the trial drug. Based on the current data, however, the likelihood of seeing any difference in outcomes between the two groups was

unlikely. Finally, 21 (4%) patients received open-label steroids though this is unlikely to have materially affected the outcome.

In summary, hydrocortisone did not decrease mortality in a general septic shock population despite hastening shock reversal. This lack of improvement may be related to an increased incidence of superinfections and new septic episodes. No benefit was seen in the corticotropin nonresponder subgroup, as was shown previously for patients with severe septic shock. This may be related to methodological issues surrounding the accurate diagnosis of adrenal insufficiency in the critically ill or to a decreased prognostic importance of this phenomenon in less severe shock. The short corticotropin test is not useful in guiding steroid therapy. On the basis of these findings, hydrocortisone cannot be recommended as general adjuvant therapy for septic shock (vasopressor responsive), nor can corticotropin testing to determine who should receive it. Hydrocortisone may have a role in patients treated early after the onset of septic shock who remain hypotensive despite high dose vasopressors (vasopressor unresponsive). [16]

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Table 1. Demographic characteristics of 499 septic shock patients at baseline.

Characteristic	**Non Responders**		**Responders**		**All patients**	
	Hydrocortisone	Placebo	Hydrocortisone	Placebo	Hydrocortisone	Placebo
	(N = 125)	(N = 108)	(N = 118)	(N = 136)	(N = 251)	(N = 248)
Age, mean ± SD (yr)	63 ± 13	63 ± 15	62 ± 14	64 ± 16	63 ± 14	63 ± 15
Sex - Male	85 (68)	69 (64)	76 (64)	95 (70)	166 (66)	166 (67)
Female	40 (32)	39 (36)	42 (36)	41 (30)	85 (34)	82 (33)
Race- Caucasian Ω	119 (95)	101 (94)	110 (93)	125 (92)	236 (94)	228 (92)
Prior or pre-existing disease						
- Hypertension	48 (38)	37 (34)	39 (33)	60 (44) §	89 (36)	98 (40) §
- Coronary Artery Disease	20 (16)	26 (24)	17 (14)	21 (15) §	37 (15)	47 (19) §

- Congestive Heart Failure	5 (4)	8 (7)	4 (3)	12 (9) §	10 (4)	20 (8) §
- Neurological Disease	19 (15)	10 (9)	14 (12)	14 (10) §	33 (13)	25 (10) §
- COPD	14 (11)	12 (11)	11 (9)	17 (13) §	27 (11)	29 (12) §
- Other pulmonary disorder	6 (5)	12 (11)	17 (14)	12 (9) §	23 (9)	24 (10) §
Cancer	27 (22)	21 (19)	18 (15)	16 (12) §	47 (19)	37 (15) §
Diabetes	22 (18)	19 (18)	28 (24)	37 (27) §	51 (20)	56 (23) §
Liver Disease	14 (11)	10 (9)	9 (8)	7 (5) §	23 (9)	17 (7) §
Chronic renal failure	12 (10)	11 (10)	10 (9)	10 (7) §	22 (9)	21 (9) §
Admission category						
Medical	39 (31)	35 (32) *	37 (31) †	57 (42) *	80 (32) †	93 (38) †
Emergency surgery	69 (55)	63 (58) *	66(56) †	67 (49) *	138 (55) †	132 (55) †

Elective surgery	17 (14)	9 (8) *	13 (11) †	11 (8) *	31 (12) †	21 (9) †

Data are means±SD for continuous variables or numbers of patients (percentages) for categorical variables.

COPD = chronic obstructive pulmonary disease

*- 1 missing value, † - 2 missing values, § - 3 missing values

Ω- Race- was ascertained by health care personnel

Table 2. Clinical characteristics of 499 septic shock patients at baseline

Characteristic	**Non Responders**		**Responders**		**All patients**	
	Hydrocortisone (N = 125)	Placebo (N = 108)	Hydrocortisone (N = 118)	Placebo (N = 136)	Hydrocortisone (N = 251)	Placebo (N = 248)
Temperature (℃)	37.7 ± 1.6*	37.9 ± 1.6	38.0 ± 1.4†	38.1 ± 1.3*	37.9 ± 1.5§	38.0 ± 1.4*
Heart rate (beats/min)	121 ± 24*	119 ± 23	116 ± 29§	117 ± 26	119 ± 26 Ω	118 ± 25
Systolic blood pressure (mm Hg)	92 ± 22*	97 ± 25	94 ± 24†	95 ± 29	94 ± 23§	95 ± 27
SAPS II	50.7 ± 17.8	49.0 ± 16.3	47.9 ± 18.0*	48.4 ± 16.9	49.5 ± 17.8*	48.6 ± 16.7
SOFA Score	11.0 ± 3.4	10.7 ± 3.4	10.3 ± 3.4	10.5 ± 2.9	10.6 ± 3.4	10.6 ± 3.2

Leukocytes (x10^3/mm^3)	15.8 ± 11.2Ω	13.8 ± 9.8†	14.3 ± 8.1 Ω	15.4 ± 9.8§	14.9 ± 9.8α	14.7 ± 9.8‡
Platelets (x10^3/mm^3)	205 ± 131 Ω	200 ± 150†	218 ± 140 Ω	203 ± 119 Ω	218 ± 140α	203 ± 119¶
Glucose (mg/dl)	140 ± 65 α	126 ± 52¶	139 ± 59¥	146 ± 45§	140 ± 65!	137 ± 50β
Arterial lactate (mmol/l)	4.6 ± 4.0θ	4.0 ± 3.9γ	3.1 ± 3.0γ	4.1 ± 4.0δ	3.9 ± 3.6††	4.1 ± 4.1**
PaO_2/FiO_2 (mm Hg)	159 ± 89£	161 ± 72γ	162 ± 82#	149 ± 73€	162 ± 89	154 ± 73Ψ
Cortisol (µg/dl)						
- Before corticotrophin	30 ± 20	29 ± 19	27 ± 19	29 ± 21	28 ± 20 α	29 ± 20 Ω
- 60 minutes after corticotropin	33 ± 19	32 ± 18	46 ± 22	46 ± 23	39 ± 22 α	39 ± 22 Ω
- Response to corticotropin test	3 ±4	3 ± 4	18 ± 11	16 ± 6	11 ± 11 α	10 ± 8 Ω
On vasopressor/inotrope at baseline	125 (100)	108 (100)	117 (99)	131 (96)	249 (99)	243 (98)

Vasopressor-** number, (percent of patients receiving drug), and maximum dose (µg/kg/min)						
- norepinephrine	116 (93)	104 (96)	103 (87)	124 (91)	224 (89)	231 (93)
	0.5 ± 0.5	0.5 ± 0.5	0.4 ± 0.7	0.4 ± 0.5	0.5 ± 0.6	0.4 ± 0.5
- epinephrine	19 (15)	9 (8)	14 (12)	13 (10)	35 (14)	22 (9)
	0.8 ± 1.6	0.2 ± 0.1	0.3 ± 0.4	1.4 ± 3.3	0.6 ± 1. 2	0.9 ± 2.6
- dopamine	10 (8)	9 (8)	16 (14)	19 (14)	27 (11)	29 (12)
	12.9 ± 9.6	7.1 ± 6.3	9.8 ± 6.1	8.3 ± 7.1	10.4 ± 7.5	7.9 ± 6.6
Ventilatory support at baseline						

Mechanical ventilation	113 (90)	99 (92)	108 (91)	110 (81)	228 (90)	212 (86)
Tidal Volume (ml/kg)	7.6 ± 2.1γ	7.5 ± 2.1#	7.6 ± 2.2π	7.7 ± 2.2π	7.7 ± 2.1	7.6 ± 2.1Ψ
FiO_2 (%)	67 ± 25 α	64 ± 25 Ω	60 ± 24μ	63 ± 24ω	64 ± 25&	63 ± 24!
PEEP (cm H_2O)	8 ± 4‡	8 ± 3¥	9 ± 4 β	9 ± 4	9 ± 4π	9 ± 4§
Activated protein C §§	11(9)	13 (12)	6 (5)	7 (5)	17 (7)	20 (8)
Antithrombin III §§	24 (19)	17 (16)	15 (13)	19 (14)	40 (16)	36 (15)

Data are shown as mean±SD for continuous variables or numbers of patients (percentages) for categorical variables.

SAPS II - Simplified Acute Physiology Score II; scores range from 0- 163, with higher scores indicating greater severity. SOFA - Sequential-related organ failure assessment; scores range from 0-24, with higher scores indicating greater organ system failure. PaO_2 - arterial oxygen

pressure. FiO_2 : inspired oxygen fraction. PEEP- positive end expiration pressure. Tidal volume and PEEP missing values from ventilated patients. ** 5 patients received vasopressin, 4 in the steroid group and 1 placebo patient.

*-1 missing value, † - 2 missing values, §- 3 missing values, Ω- 4 missing values, ‡- 5 missing values, ¶- 6 missing values, ¥- 7 missing values, α - 8 missing values, β - 9 missing values, ω- 11 missing values, µ- 12 missing values, π- 13 missing values, γ - 14 missing values, ¦- 16 missing values, €- 17 missing values, £- 18 missing values, # - 19 missing values, &-20 missing values, δ -22 missing values, θ - 23 missing values, Ψ- 32 missing values, **- 36 missing values, ††- 49 missing values, §§- patients may have received these drugs after baseline.

Cortisol: 1µg/dL = 27.59 nmol/L; PaO_2/FiO_2 1 mm Hg= 7.5 kPa; Glucose 1 mg/dl = 0.0555 mmol/L

Table 3. Outcome in 499 septic shock patients

	Non responders		*P* value	Responders		*P* value	All patients		*P* value
	HC (N = 125)	Placebo (N = 108)		HC (N = 118)	Placebo (N = 136)		HC (N = 251)	Placebo (N = 248)	
28-day mortality	49 (39.2)	39 (36.1)	0.69	34 (28.8)	39 (28.7)	1.00	86 (34.3)	78 (31.5)	0.51
RR differences	1.09 (0.77-1.52)			1.00 (0.68-1.48)			1.09 (0.84-1.41)		
Difference HC- Placebo	3.1% [-9.5 to 15.7%]			0.1% [-11.2 to 11.4%]			2.8% [-5.5 to 11.2%]		
ICU mortality	58 (46.4)	44 (40.7)	0.43	41 (34.7)	45 (33.3) *	0.89	102 (40.6)	89 (36.0) *	0.31
RR differences	1.14 (0.85-1.53)			1.04 (0.74-1.47)			1.13 (0.90-1.41)		
Difference HC- Placebo	5.7% [-7.1 to 18.4%]			1.4% [-10.3 to 13.1%]			4.6% [-3.9 to 13.1%]		

Hospital mortality	60 (48.0)	50 (46.3)	0.90	48 (40.7)	50 (37.6) §	0.70	111 (44.2)	100 (40.8) §	0.47
RR differences	1.04 (0.79-1.36)			1.08 (0.79-1.47)			1.08 (0.88-1.33)		
Difference HC- Placebo	1.7% [-11.1 to 14.6%]			3.1% [-9.0 to 15.2%]			3.4% [-5.3 to 12.1%]		
1-year mortality	73 (58.9) *	60 (57.1)§	0. 89	61 (55.0)¥	67 (53.2)ω	0.80	137 (56.6)β	127 (54.0)π	0.58
RR differences	1.03 (0.83-1.29)			1.03 (0.82-1.31)			1.05 (0.89-1.23)		
ICU Length of stay (days)	17 ± 19	17 ± 17	0.47	18 ± 22	19 ± 16*	0.26	19 ± 31	18 ± 17*	0.51
Hospital Length of stay (days)	29 ± 26	31 ± 27	0.82	36 ± 40	35 ± 43§	0.68	34 ± 41	34 ± 37§	0.47

Data are numbers of deaths (percentages) and odds (RR) ratios (95% confidence intervals). p-values for categorial variables: Fisher's exact test, p-values for continuous variables: Wilcoxon rank sum test. HC = hydrocortisone, ICU = intensive care unit. *-1 missing value, † - 2 missing values, §- 3 missing values, ¥- 7 missing values, β - 9 missing values, ω- 10 missing values, π- 13 missing values.

Table 4. Adverse events in 466 septic shock patients (Per protocol population)

Event	Hydrocortisone (N = 234)	Placebo (N = 232)	RR differences
1. Superinfections	78 (33)	61 (26)	1.27 (0.96-1.68)
- Catheter-related infection	3 (1)	3 (1)	0.99 (0.20-4.86)
- Lung infection	34 (15)	30 (13)	1.12 (0.71-1.77)
- Gastrointestinal infection	22 (9)	19 (8)	1.15 (0.64-2.06)
- Urinary tract infection	11 (5)	10 (4)	1.09 (0.47-2.52)
- Wound infection	9 (4)	7 (3)	1.27 (0.48-3.37)

- Other infection	16 (7)	8 (3)	1.98 (0.87-4.54)
- New Sepsis	6 (3)	2 (1)	2.97 (0.61-14.59)
- New Septic shock	14 (6)	5 (2)	2.78 (1.02-7.58)
2. Other adverse events	85 (34)	63 (25)	
- Anastomotic leak	4 (2)	4 (2)	0.99 (0.25-3.92)
- Wound dehiscence	2 (1)	2 (1)	0.99 (0.14-6.98)
- Repeat Shock	84 (34)	62 (25)	1.34 (1.01-1.77)
- Bleeding – Any	21 (9)	16 (7)	1.30 (0.70-2.43)
- Bleeding – Gastrointestinal	15 (6)	13 (6)	1.14 (0.56-2.35)

- Critical illness polyneuropathy	2 (1)	4 (2)	0.50 (0.09-2.68)
- Multiple organ system failure	34 (15)	33 (14)	1.02 (0.66-1.59)
- Refractory shock	20 (9)	25 (11)	0.79 (0.45-1.39)
- Pulmonary	8 (3)	13 (6)	0.61 (0.26-1.44)
- Renal	7 (3)	6 (3)	1.16 (0.39-3.39)
- Neurologic	1 (0)	1 (0)	0.99 (0.06-15.76)
- Hyperglycemia (Glucose ≥150 mg/dl on any day between day 1 & day 7)	186(85)	161 (72)	1.18 (1.07-1.31)
- Hypernatremia – (Sodium ≥150 mEq/L on any day between day 1 & day 7)	67 (29)	42 (18)	1.58 (1.13-2.22)

3. Possibly related to shock			
- Stroke	3 (1)	1 (0)	2.97 (0.31-28.39)
- Acute myocardial infarction	14 (6)	13 (6)	1.24 (0.34-4.56)
- Peripheral limb ischemia	-	1 (0)	

Data shown as numbers (percentages) and odds (RR) ratios (95% confidence intervals).

An individual patient can have more than one adverse event

Glucose 150 mg/dl = 8.3 mmol/L

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APPENDIX

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Figure legends:

Figure 1. Study enrollment and analysis.

Figure 2. Kaplan Meier Curves for 28 day all cause mortality in (a) corticotropin nonresponders (b) corticotropin responders and (c) all patients

Figure 3. Kaplan Meier Curves for time to reversal of shock in (a) corticotropin nonresponders (b) corticotropin responders and (c) all patients.