ANESTHESIOLOGY

Hydrocortisone Compared with Placebo in Patients with Septic Shock Satisfying the Sepsis-3 Diagnostic Criteria and APROCCHSS Study Inclusion Criteria

A *Post Hoc* Analysis of the ADRENAL Trial

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ANESTHESIOLOGY 2019; 131:1292–300

ABSTRACT

Background: Two recent randomized controlled trials (Adjunctive Glucocorticoid Therapy in Patients with Septic Shock [ADRENAL] and Activated Protein C and Corticosteroids for Human Septic Shock [APROCCHSS]) of corticosteroids in patients with septic shock reported different treatment effects on 90-day mortality. Both trials enrolled patients who met the criteria for septic shock using the second international consensus definitions for sepsis and septic shock (Sepsis-2), but the APROCCHSS trial mandated a greater severity of shock as an inclusion criterion.

Methods: The authors conducted *post hoc* sensitivity analyses of the ADRENAL trial to determine the effects of hydrocortisone *versus* placebo in subgroups selected using third international consensus definitions for sepsis and septic shock (Sepsis-3) diagnostic criteria or APROCCHSS inclusion criteria.

Results: There were 1,950 subjects (973 hydrocortisone and 977 placebo) who met the Sepsis-3 criteria (ADRENAL–Sepsis-3 cohort) and 905 patients (455 hydrocortisone and 450 placebo) who met the APROCCHSS criteria (ADRENAL–APROCCHSS cohort). At 90 days after randomization, in the ADRENAL–Sepsis-3 cohort, 312 of 963 (32.4%) and 337 of 958 (35.2%) patients assigned to hydrocortisone and placebo, respectively, had died (odds ratio, 0.86; 95% CI, 0.70 to 1.06; $P = 0.166$). The corresponding figures for the ADRENAL–APROCCHSS cohorts were 187 of 453 (41.3%) and 200 of 445 (44.9%), respectively (odds ratio, 0.84; 95% CI, 0.60 to 1.17; $P = 0.303$). There was no statistically significant difference in the time to death between the groups during the 90 days after randomization (hazard ratio = 0.87; 95% CI, 0.75 to 1.02; $P = 0.082$ for ADRENAL–Sepsis-3; and hazard ratio = 0.86; 95% CI, 0.71 to 1.06; $P = 0.156$ for ADRENAL–APROCCHSS cohorts). In both cohorts, patients assigned to hydrocortisone had faster resolution of shock. In the ADRENAL–Sepsis-3 cohort, patients assigned to hydrocortisone had an increase in the number of days alive and free of mechanical ventilation (57.0 ± 37.2 *vs.* 53.7 ± 38.2 days; 95% CI, 0.40 to 7.04; $P = 0.028$) and the number of days alive and free of the intensive care unit (54.3 ± 36.0 *vs.* 51.0 ± 37.1; 95% CI, 0.82 to 7.24; $P = 0.014$).

Conclusions: In a *post hoc* analysis of the ADRENAL trial participants who fulfilled either the Sepsis-3 or the APROCCHSS inclusion criteria, a continuous infusion of hydrocortisone did not result in a lower 90-day mortality than placebo in septic shock.

(ANESTHESIOLOGY 2019; 131:1292–300)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Definitions and management strategies for septic shock continue to be updated as defined in Sepsis-2, Sepsis-3, and other guidelines
- Recent randomized controlled trials of corticosteroids in septic shock report different treatment effects on 90-day mortality but use different inclusion criteria

What This Article Tells Us That Is New

- In a *post hoc* analysis of the Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial, in participants who fulfilled either the Sepsis-3 or -2 inclusion criteria or those with severe septic shock, a continuous infusion of hydrocortisone did not result in a lower 90-day mortality than placebo

Two recent large randomized controlled trials (Adjunctive Glucocorticoid Therapy in Patients with Septic Shock [ADRENAL] and Activated Protein C and Corticosteroids for Human Septic Shock [APROCCHSS]) have added substantial new data to inform opinion regarding the use of corticosteroids in patients with septic shock.[1,2] The ADRENAL trial (N = 3,800) investigated the role of 200 mg per day of hydrocortisone by infusion for 7 days compared with placebo and reported no significant difference between groups with

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 Anesthesiology 2019; 131:1292–300. DOI: 10.1097/ALN.0000000000002955

respect to 90-day mortality (27.9% *vs.* 28.8%), but patients assigned to hydrocortisone had earlier shock reversal and liberation from mechanical ventilation.[1] The trial used the second international consensus definitions for sepsis and septic shock (Sepsis-2)[3] and additionally mandated a minimum duration of 4 h of vasopressor therapy and the need for mechanical ventilation to be eligible for enrollment.

In 2016, subsequent to the commencement of the ADRENAL trial, a third international task force provided an updated consensus definition of sepsis and septic shock, termed Sepsis-3[4]. It is unclear whether the use of Sepsis-3 criteria for enrolling patients into the ADRENAL trial would have influenced the trial results and resulted in different conclusions.

The APROCCHSS trial[2] (N = 1,241) examined the effect of 200 mg per day of hydrocortisone administered in divided doses, combined with oral fludrocortisone compared with placebo in patients with severe septic shock and reported improved 90-day mortality in the steroid group (43.0% *vs.* 49.1%), coupled with earlier shock reversal and liberation from mechanical ventilation. The two trials differed with respect to trial design, inclusion–exclusion criteria, mode of administration of hydrocortisone (infusion *vs.* bolus), and use of fludrocortisone. Attention has focused on the inclusion criteria of the two trials and whether the different treatment effect was because of a sicker cohort of patients in the APROCCHSS group.

We hypothesized that hydrocortisone may have beneficial effects on mortality in the sicker cohort of patients with septic shock. We therefore conducted *post hoc* subgroup analyses of the ADRENAL trial to determine whether the application of the Sepsis-3 or the APROCCHSS inclusion criteria to the study population would have resulted in different treatment effects between the hydrocortisone and the placebo groups.

Materials and Methods

Study Design and Research

We conducted a *post hoc* analysis of the ADRENAL database to identify patient cohorts who met Sepsis-3 criteria (ADRENAL–Sepsis-3) for septic shock or the APROCCHSS (ADRENAL–APROCCHSS) inclusion criteria. A detailed description of the study methods, outcomes, statistical analysis, and the results for the ADRENAL trial has already been published.[5] In brief, the ADRENAL trial enrolled mechanically ventilated patients with septic shock who required a minimum duration of 4 h of vasopressor therapy. The APROCCHSS trial enrolled patients with septic shock with organ failure criteria and who required a minimum duration of 6 h of vasopressor therapy and doses of norepinephrine of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The key aspects of and the differences in the inclusion–exclusion criteria and interventions for the ADRENAL and APROCCHSS trials are listed in Supplemental Digital Content 1 (http://links.lww.com/ALN/C48). To identify patients for inclusion in the analyses, we performed two separate interrogations of the ADRENAL database as outlined below.

ADRENAL–Sepsis-3 Analysis. Patients were selected using the following criteria: subjects who had (1) a mean arterial pressure (MAP) of less than 65 mmHg in the 24 h preceding randomization and (2) a plasma lactate concentration of more than 2 mmol.

ADRENAL–APROCCHSS Analysis. Patients were selected using the following criteria: patients receiving (1) more than 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of catecholamines at baseline and (2) any one of the following criteria for organ failure: partial pressure of arterial oxygen tension/fraction of inspired oxygen concentration ratio less than 200, or platelets less than 50×10^9/l, or bilirubin more than 102 μmol/l, or creatinine of more than 300 μmol/l.

Statistical Analysis and Outcome Measures

Of the original cohort of 3,800 patients, 1,950 met the Sepsis-3 criteria, and 905 met the APROCCHSS criteria. We determined that a sample size of 1,950 in the ADRENAL–Sepsis-3 cohort provided 90% power to detect an absolute difference of 7% and 80% power to detect an absolute difference of 6%, assuming 35% mortality rate in control group. In the ADRENAL–APROCCHSS cohort, a sample size of 905 provided 90% power to detect an absolute difference of 11% and 80% power to detect an absolute difference of 9%, assuming a baseline mortality of 45%. We applied the same statistical methods as described in the original ADRENAL trial and used the same set of primary and secondary outcomes. For the primary outcome of mortality at day 90, to account for stratification variables, the main analysis was performed using logistic regression with treatment allocation and admission type (medical or surgical) as fixed effects and trial site as a random effect. For secondary binary and continuous outcomes, logistic regression and linear regression were used, respectively, depending on the type of outcomes, including treatment allocation and admission type as fixed effect and site as a random effect. These were described in detail in a statistical analysis plan published before database lock of the ADRENAL trial.[5] All

Submitted for publication February 1, 2019. Accepted for publication July 16, 2019.
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tests were conducted with statistical significant level of 0.05 (type 1 error), and significant test results are hypothesis-generating. No adjustments for multiplicity of testing were applied, but significant test results were interpreted in light of the multiple comparisons made.

We also applied the analytical methods as reported in the APROCCHSS article[6] on the ADRENAL–APROCCHSS cohort to assess the treatment effect on the primary outcome, using relative risk without adjustment of stratification factor and trial site. We also performed survival analysis of time to death using same approach as described for the ADRENAL trial. Time to death was reported using Kaplan–Meier plots with differences in survival tested using a Cox proportional hazard model[7] including the randomized treatment arm, admission type, and a random-center effect. Proportional hazard assumptions were tested by adding the interaction term between time and treatment in the Cox regression model. We used SAS Enterprise Guide 7.15 software for statistical analysis (SAS institute, Australia).

Results

Of the original cohort of 3,800 patients in ADRENAL, there were 1,950 (51.3%) subjects who met the Sepsis-3 criteria: 973 assigned to hydrocortisone and 977 assigned to placebo. Of these subjects, 905 (23.8%) patients met the APROCCHSS criteria: 455 assigned to hydrocortisone and 450 assigned to placebo. The patient flow chart is shown in Supplemental Digital Content 2 (http://links.lww.com/ALN/C49).

The baseline characteristics of all ADRENAL participants as well as the cohorts meeting Sepsis-3 and APROCCHSS criteria are reported in table 1. The three groups were similar at baseline with respect to demographic characteristics, admission diagnoses, sources of sepsis, baseline interventions, and illness severity. Patients in the ADRENAL–Sepsis-3 and ADRENAL–APROCCHSS cohorts had higher mean baseline plasma lactate concentration than the original ADRENAL cohort. There was higher proportion of medical admissions and more patients treated with renal replacement therapy at baseline in the ADRENAL–APROCCHSS cohort than in the ADRENAL cohort.

Outcomes

Primary Outcome. At 90 days after randomization, in the ADRENAL–Sepsis-3 cohort, 312 of 963 (32.4%) of the patients assigned to hydrocortisone and 337 of 958 (35.2%) of the patients assigned to placebo had died (odds ratio, 0.86; 95% CI, 0.70 to 1.06; $P = 0.166$; table 2). The corresponding figures for the ADRENAL–APROCCHSS cohorts were 187 of 453 (41.3%) and 200 of 445 (44.9%), respectively, for hydrocortisone and the placebo groups (odds ratio, 0.84; 95% CI, 0.60 to 1.17; $P = 0.303$). We conducted an additional *post hoc* analysis of the primary outcome in the ADRENAL–APROCCHSS cohort who were randomized after 6 h of vasopressor therapy. Of the 905 patients in the ADRENAL–APROCCHSS, 730 patients were randomized after 6 h of pressor therapy (365 in each group). The 90-day mortality rates were 42% (153 of 365) and 46.1% (168 of 365) in the hydrocortisone and placebo groups, respectively (odds ratio, 0.83; 95% CI, 0.60 to 1.16; $P = 0.306$). When the original ADRENAL data and the ADRENAL–APROCCHSS cohorts were analyzed using the APROCCHSS approach as rate ratios, there were no statistically significant differences in the primary outcome between the treatment groups (Supplemental Digital Content 1, http://links.lww.com/ALN/C48). There was no statistically significant difference in the time to death between the groups during the 90days after randomization (hazard ratio = 0.87; 95% CI, 0.75 to 1.02; $P = 0.082$ for the ADRENAL–Sepsis-3 cohort; and hazard ratio = 0.86; 95% CI, 0.71 to 1.06; $P = 0.156$ for the ADRENAL–APROCCHSS cohort; figs. 1 and 2).

Secondary Outcomes.

ADRENAL–Sepsis-3. There was a statistically significant difference in day-28 mortality between the two groups 26.7% (259 of 969) *versus* 31% (300 of 968) in the hydrocortisone and placebo groups, respectively (odds ratio, 0.80; 95% CI, 0.64 to 0.99; $P = 0.042$). Patients assigned to hydrocortisone had faster resolution of shock (median [interquartile range], 3 [2 to 6] *vs.* 5 [3 to 12] days; hazard ratio = 1.36; 95% CI, 1.23 to 1.50; $P < 0.0001$), a higher frequency of recurrence of shock (22.1% [214 of 970] *vs.* 17.4% [170 of 977]; odds ratio, 1.35; 95% CI, 1.08 to 1.69; $P = 0.009$), an increase in the number of days alive and free of mechanical ventilation (57.0 ± 37.2 *vs.* 53.7 ± 38.2 days; 95% CI, 0.40 to 7.04; $P = 0.028$), an increase in the number of days alive and free of renal replacement therapy (60.9 ± 38.2 *vs.* 57.2 ± 39.6 days; 95% CI, 0.57 to 7.43; $P = 0.022$), and an increase in the number of days alive and free of the intensive care unit (54.3 ± 36.0 *vs.* 51.0 ± 37.1; 95% CI, 0.82 to 7.24; $P = 0.014$). There were no significant differences with respect to the development of new onset bacteremia or fungemia, in the proportions of patients requiring blood transfusions, in days alive and out of hospital, or in time to hospital discharge between the groups.

ADRENAL–APROCCHSS. There was no statistically significant difference in day-28 mortality between the two groups (36.6% [166 of 454] *vs.* 40.3% [181 of 449] in the hydrocortisone and placebo groups, respectively; odds ratio, 0.84; 95% CI, 0.62 to 1.13; $P = 0.251$). Patients assigned to hydrocortisone had a faster resolution of shock (median [interquartile range], 4 [3 to 41] *vs.* 7 [3 to unavailable value] days; hazard ratio = 1.27; 95% CI, 1.09 to 1.48; $P = 0.002$) but a higher frequency of recurrence of shock (23.3% [106 or 455] *vs.* 16.2% [73 of 450]; odds ratio, 1.57; 95% CI, 1.12 to 2.18; $P = 0.008$).

There were no statistically significant differences with respect to the number of days alive and free of

Table 1. Baseline Patient Characteristics

Characteristic	ADRENAL		ADRENAL (Sepsis-3)		ADRENAL–APROCCHSS		APROCCHSS	
	Hydrocortisone (N = 1,853)	Placebo (N = 1,860)	Hydrocortisone (N = 973)	Placebo (N = 977)	Hydrocortisone (N = 455)	Placebo (N = 450)	Hydrocortisone (N = 614)	Placebo (N = 627)
Age, yr	62 ± 15	63 ± 15	62 ± 15	64 ± 15	63 ± 14	62 ± 15.0	66 ± 14	66 ± 15
Male sex	1,119/1,853 (60.4)	1,140/1,860 (61.3)	558/973 (57.3%)	577/977 (59.1%)	271/455 (59.6%)	266/450 (59.1%)	402/614 (65.5%)	424/626 (67.7%)
Weight, kg	85.8 ± 26.6	85.6 ± 26.3	84.9 (26.58)	84.4 (25.59)	79.9 ± 22.4	78.7 ± 22.1	74 ± 19	75 ± 20
Admission type								
Medical	1,273/1,849 (68.8)	1,266/1,857 (68.2)	676/973 (69.5%)	657/977 (67.2%)	355/455 (78.0%)	342/450 (76.0%)	495/601 (75.5%)	499/616 (81%)
Surgical	576/1,849 (31.2)	591/1,857 (31.8)	297/973 (30.5%)	320/977 (32.8%)	100/455 (22.0%)	108/450 (24.0%)	106/601 (24.5%)	117/616 (19%)
APACHE II (median IQR)	24.0 (19.0 to 29.0)	23.0 (18.0 to 29.0)	25.0 (20.0 to 30.0)	25.0 (20.0 to 30.0)	27.0 (22.0 to 31.0)	26.0 (22.0 to 31.0)	N/A	N/A
Baseline therapies								
Mechanical ventilation	1,845/1,849 (99.8)	1,855/1,857 (99.9)	970/973 (99.7%)	976/977 (99.9%)	454/455 (99.8%)	450/450 (100%)	567/614 (91.3%)	569/623 (92.3%)
Inotropes/vasopressors								
Norepinephrine	1,823/1,853 (98.4)	1,821/1,860 (97.9)	958/973 (98.5%)	962/977 (98.5%)	454/455 (99.8%)	450/450 (100%)	534/590 (90.5%)	552/595 (92.8%)
Vasopressin	280/1,853 (15.1)	321/1,860 (17.3)	196/973 (20.1%)	234/977 (24.0%)	120/455 (26.4%)	155/450 (34.4%)	0/577 (0.0%)	1/580 (0.2%)
Epinephrine	134/1,853 (7.2)	113/1,860 (6.1)	109/973 (11.2%)	94/977 (9.6%)	62/455 (13.6%)	51/450 (11.3%)	53/585 (9.1%)	58/582 (10.0%)
Others	157/1,853 (8.5)	173/1,860 (9.3)	85/973 (8.7%)	113/977 (11.6%)	47/455 (10.3%)	55/450 (12.2%)	86/584 (14.7%)	100/584 (17.1%)
Antimicrobials	1,817/1,848 (98.3)	1,821/1,857 (98.1)	956/972 (98.4%)	962/977 (98.5%)	446/454 (98.2%)	445/450 (98.9%)	595/614 (96.9%)	602/626 (96.2%)
Renal replacement therapy	228/1,849 (12.3)	242/1,857 (13.0)	136/973 (14.0%)	159/977 (16.3%)	97/455 (21.3%)	90/450 (20.0%)	161/596 (27.0%)	168/598 (28.1%)
Physiologic variables								
Heart rate, beats/min	96.0 ± 21.6	95.0 ± 20.9	100.2 ± 21.67	98.0 ± 21.63	105.5 ± 23	101.5 ± 21.6	N/A	N/A
MAP, mmHg	72.5 ± 8.2	72.2 ± 8.3	71.6 ± 8.4	71.0 ± 8.2	71.0 ± 8.6	71.0 ± 8.8	N/A	N/A
CVP, mmHg	12.0 ± 5.2	12.1 ± 5.3	12.1 ± 5.3	12.6 ± 5.5	12.6 ± 5.5	12.8 ± 5.5	N/A	N/A
Lowest MAP	57.3 ± 8.5	57.1 ± 9.1	53.9 ± 7.6	53.4 ± 8.4	55.4 ± 8.6	54.6 ± 9.8	N/A	N/A
Highest lactate, mmol/l	3.8 ± 3.2	3.8 ± 3.1	5.2 ± 3.4	5.0 ± 3.2	5.2 ± 4.0	5.2 ± 3.7	4.4 ± 5.2	4.3 ± 4.6
Highest bilirubin, mg/dl	1.7 ± 2.4	1.7 ± 2.4	2.0 ± 2.7	1.9 ± 2.9	1.9 ± 2.2	2.05 ± 3.3	N/A	N/A
Highest creatinine, mg/dl	2.2 ± 2.0	2.1 ± 1.7	2.3 ± 1.9	2.3 ±1.6	2.7 ± 2.3	2.5 ± 2.0	N/A	N/A
Lowest PaO_2/FiO_2	164.6 ± 91.3	166.4 ± 91.9	157.9 ± 89.2	160.1 ± 90.6	122.0 ± 60.6	126.3 ± 66.0	190 ± 100	197 ± 102
Highest white cell count, 10^9/l	17.4 ± 11.4	17.8 ± 14.7	17.5 ± 12.0	17.7 ± 15.9	17.2 ± 13.2	17.6 ± 19.9)	N/A	N/A
Primary site of infection								
Pulmonary	623/1,844 (33.8)	677/1,854 (36.5)	289/970 (29.8%)	324/976 (33.2%)	169/453 (37.3%)	179/450 (39.8%)	373/614 (60.7%)	363/626 (58.0%)
Abdominal	477/1,844 (25.9)	467/1,854 (25.2)	221/970 (22.8%)	225/976 (23.1%)	83/453 (18.3%)	96/450 (21.3%)	74/614 (12.1%)	68/626 (10.9%)
Blood	316/1,844 (17.1)	325/1,854 (17.5)	185/970 (19.1%)	188/976 (19.3%)	93/453 (20.5%)	83/450 (18.4%)	225/614 (36.6%)	229/626 (36.6%)
Skin/soft tissue	137/1,844 (7.4)	116/1,854 (6.3)	72/970 (7.4%)	59/976 (6.0%)	21/453 (4.6%)	21/450 (4.7%)	23/626 (3.7%)	29/614 (4.7%)
Urinary	146/1,844 (7.9)	133/1,854 (7.2)	83/970 (8.6%)	74/976 (7.6%)	41/453 (9.1%)	27/450 (6.0%)	N/A	N/A
Others	145/1,844 (7.9)	136/1,854 (7.3)	52/970 (5.4%)	47/976 (4.8%)	21/453 (4.6%)	22/450 (4.9%)	11/614 (1.8%)	18/626 (2.9%)
ICU admission to randomization, h	26.1 ± 70.7	28.9 ± 72.8	20.0 ± 32.2	23.3 ± 51.4	19.8 ± 31.4	23.0 ± 36.6	72 ± 216	72 ± 312
Shock to randomization, h	20.9 ± 91.9	21.2 ± 83.4	21.5 ± 110.94	20.3 ± 83.3	24.0 ± 124.9	21.8 ± 102.3	N/A	N/A

Plus–minus values represent means ± standard deviations. The proportions are presented as numbers of subjects/denominator (percentage). Surgical admissions were defined as patients admitted to the ICU from the operating room or the recovery room. For the ADRENAL, ADRENAL–Sepsis-3, and ADRENAL–APROCCHSS cohorts: (1) heart rate, MAP, and CVP values represent the most recent value preceding randomization; (2) lowest values for MAP and the ratio between arterial and inspired oxygen tension (PaO_2/FiO_2) and highest values for lactate, bilirubin, creatinine, and white blood cell counts were measured during 24 h before randomization; and (3) baseline therapies denote the value in the 24 h before randomization. The data from APROCCHSS were those reported in the main article or in Supplemental Digital Content 1 (http://links.lww.com/ALN/C48). No significant differences between the groups were observed at baseline. To convert values for bilirubin to μmol/l, multiply by 17.1. To convert values for creatinine to μmol/l, multiply by 88.4.

ADRENAL, Adjunctive Glucocorticoid Therapy in Patients with Septic Shock trial; APROCHSS, Activated Protein C and Corticosteroids for Human Septic Shock trial; CVP, central venous pressure; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial pressure; N/A, not available (value not reported in the article and hence not available); Sepsis-3, third international consensus definitions for sepsis and septic shock.

Table 2. Primary Outcome Comparison: ADRENAL, ADRENAL–Sepsis-3 cohort, ADRENAL–APROCCHSS cohort, and APROCCHSS original

	Hydrocortisone	Placebo	Odds or Rate Ratio	95% CI	*P* Value
ADRENAL (original)	511/1,832 (27.9)	526/1,826 (28.8)	0.95*	0.82 to 1.10	0.504
ADRENAL–Sepsis-3	312/963 (32.4)	337/958 (35.2)	0.86*	0.70 to 1.06	0.166
ADRENAL–APROCCHSS	187/453 (41.3)	200/445 (44.9)	0.84*	0.60 to 1.17	0.303
APROCCHSS (original)	264/614 (43.0)	308/627 (49.1)	0.88†	0.78 to 0.99	0.03

The primary outcome was 90-day mortality (%) reported as odds ratios (using the statistical analytical methods described in the ADRENAL article[1,5]). The proportions are presented as number of subjects/denominator (percentage). The analysis of mortality at day 90 reported in this table, adjusted for stratification variables is a logistic regression including treatment and admission type as fixed effects and study site as a random effect.

*Odds ratios. †Rate ratios.

mechanical ventilation, the number of days alive and free of renal replacement therapy, the number of days alive and free of the intensive care unit, the development of new onset bacteremia or fungemia, in the proportions of patients requiring blood transfusions, the number of days alive and out of hospital, or the time to hospital discharge between the groups. A comparison of the secondary outcomes of the Sepsis-3 and the APROCCHSS cohorts with those of the original ADRENAL and the APROCCHSS trial participants is outlined in table 3.

Discussion

In the subsets of patients from the ADRENAL trial who met the Sepsis-3 or APROCCHSS inclusion criteria, there was a higher overall mortality rate at day 90, but the administration of hydrocortisone did not result in a significantly lower mortality as compared with placebo. This is in line with the original trial results.

There was also concordance between the three cohorts in some of the secondary outcomes: earlier time to reversal

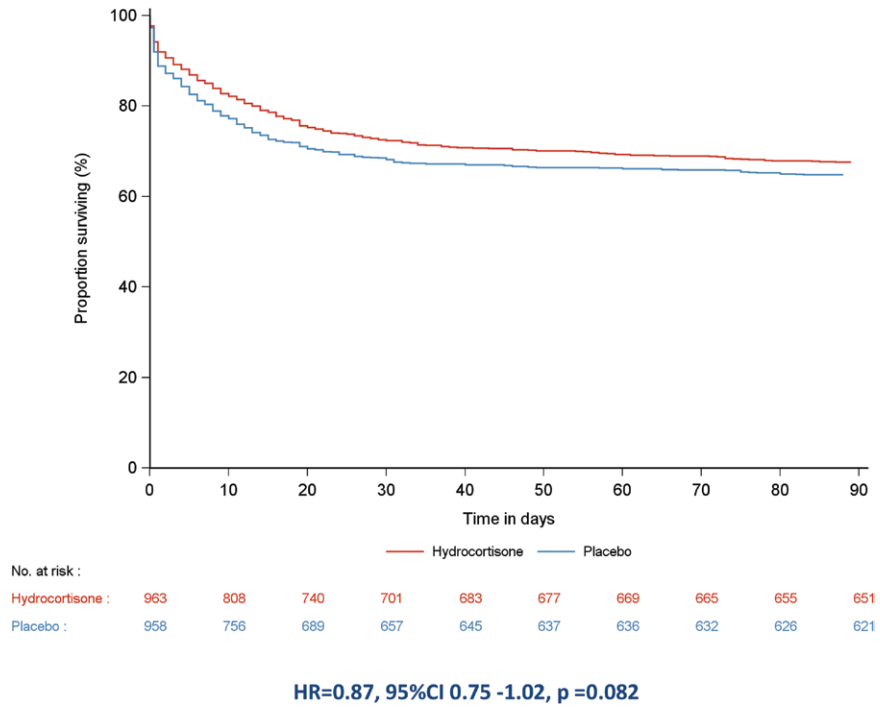

Fig. 1. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) Sepsis-3: Probability of survival and risk of death at 90 days, according to subgroup. Shown are the Kaplan–Meier estimates of the probability of survival for patients receiving either hydrocortisone or placebo. The *P* value was calculated using a Cox proportional hazard model including the randomized treatment arm, admission type, and a random-center effect. HR, hazard ratio.

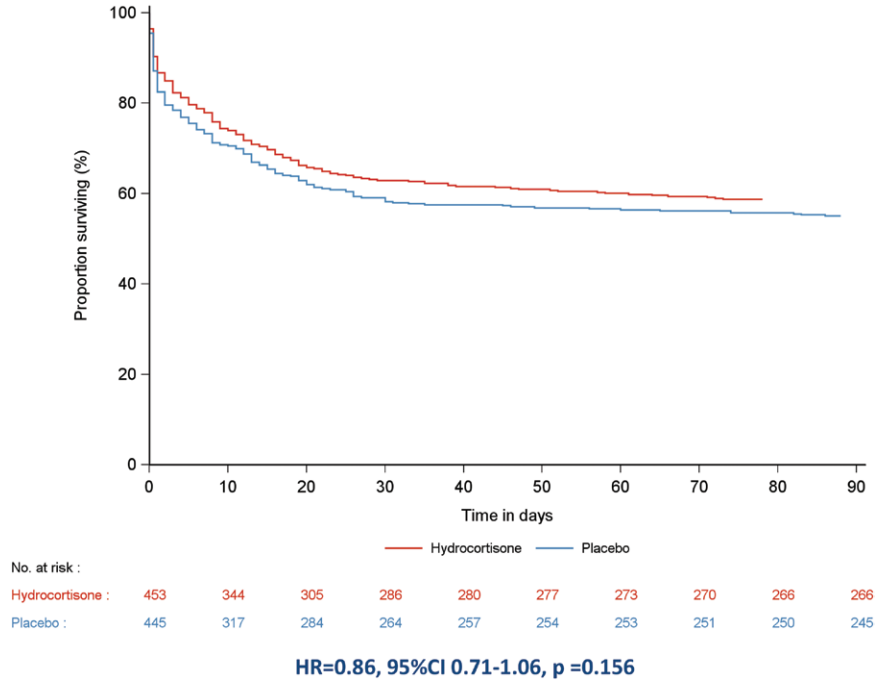

Fig. 2. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL)–Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS): Probability of survival and risk of death at 90 days, according to subgroup. Shown are the Kaplan–Meier estimates of the probability of survival for patients receiving either hydrocortisone or placebo. The *P* value was calculated using a Cox proportional hazard model including the randomized treatment arm, admission type, and a random-center effect. HR, hazard ratio.

of shock with hydrocortisone, rate of recurrence of mechanical ventilation, days alive and out of hospital, and the rate of new-onset bacteremia or fungemia. In contrast to the original trial, patients in both subsets who received hydrocortisone had a higher rate of recurrence of shock, but there was no differential treatment effect on the blood transfusion rates. In patients meeting the Sepsis-3 criteria, those assigned to hydrocortisone had reduced 28-day mortality, an increase in the number of days alive and free of mechanical ventilation and renal replacement therapy, and an increase in the number of days alive and out of the intensive care unit.

Comparisons of Mortality among ADRENAL, ADRENAL–Sepsis-3, and ADRENAL–APROCCHSS

The day-90 mortality in the ADRENAL–Sepsis-3 cohort was 33.8% (about 4 percentage points higher than the original ADRENAL cohort) but substantially lower than that predicted by the task force.[4] Of note, all the patients in the ADRENAL–Sepsis-3 cohort were mechanically ventilated, suggesting a higher degree of organ failure. Although a number of *post hoc* analyses of randomized controlled trials and registry data report mortality rates greater than 40% when Sepsis-3 criteria are applied,[8–10] other data sets have also found lower than predicted mortality rates when applying the Sepsis-3 criteria.[11–13]

The mortality rates for day 90 were comparable between the ADRENAL–APROCCHSS cohort and the original APROCCHSS cohort, although there was no different treatment effect between hydrocortisone and placebo in the ADRENAL. The other major difference between the ADRENAL and APROCCHSS was the use of fludrocortisone in the latter. It is unclear whether the use of fludrocortisone would be sufficient to explain the difference in survival. The only trial comparing hydrocortisone alone *versus* hydrocortisone plus fludrocortisone lacked adequate statistical power to identify a difference in mortality.[14] There are several reasons to doubt that the addition of fludrocortisone to the treatment regime would confer any additional benefit. Because the mineralocorticoid receptor has an equal affinity for both mineralocorticoids and glucocorticoids, a daily dose of 50 mg or more of hydrocortisone is equivalent to 0.1 mg of fludrocortisone.[15] Furthermore, the short plasma half-life (1.4 h) of fludrocortisone suggests that a single daily dose may not be optimal,[16] and there is evidence to suggest that its oral absorption is impaired in critically ill patients.[17]

In both cohorts, similar to the original trial, shock reversal occurred earlier in the hydrocortisone group, but at variance with the original ADRENAL trial results was the observation that recurrence of shock was higher in the hydrocortisone group. This finding was not reported in either of the primary studies, is an observation

Table 3. Secondary Outcomes Comparison: ADRENAL, ADRENAL–Sepsis-3 Cohort, ADRENAL–APROCCHSS Cohort, and APROCCHSS Original

	Hydrocortisone	Placebo	Odds Ratio, Hazard Ratio, Rate Ratio, or Absolute difference	95% CI	*P* Value
28-day mortality					
ADRENAL (original)	410/1,841 (22.3)	448/1,840 (24.3)	0.89*	0.76 to 1.03	0.125
ADRENAL–Sepsis-3	259/969 (26.7%)	300/968 (31.0%)	0.80*	0.64 to 0.99	0.042
ADRENAL–APROCCHSS	166/454 (36.6%)	181/449 (40.3%)	0.84*	0.62 to 1.13	0.251
APROCCHSS (original)	207/614 (33.7)	244/627 (38.9)	0.87	0.75 to 1.01	0.06
Time to reversal of shock (days); median (IQR)					
ADRENAL (original)	3 (2–5)	4 (2–9)	1.32†	1.23 to 1.41	< 0.0001
ADRENAL–Sepsis-3	3 (2–6)	5 (3–12)	1.36†	1.23 to 1.50	< 0.0001
ADRENAL–APROCCHSS	4.0 (3.0 to 41.0)	7.0 (3.0 to N/A)	1.27†	1.09 to 1.48	0.002
APROCCHSS (original)	N/A	N/A	N/A	N/A	N/A
Recurrence of shock					
ADRENAL (original)	365/1,853 (19.7)	343/1,860 (18.4)	1.07*	0.94 to 1.22	0.319
ADRENAL–Sepsis-3	214/970 (22.1%)	170/977 (17.4%)	1.35	1.08 to 1.69	0.009
ADRENAL–APROCCHSS	106/455 (23.3%)	73/450 (16.2%)	1.57	1.12 to 2.18	0.008
APROCCHSS (original)	N/A	N/A	N/A	N/A	N/A
Days alive and free of ICU					
ADRENAL (original)	58.2 ± 34.8	56.0 ± 35.4	2.26‡	0.04 to 4.49	0.047
ADRENAL–Sepsis-3	54.3 ± 36.0	51.0 ± 37.1	4.03‡	0.82 to 7.24	0.014
ADRENAL–APROCCHSS	45.9 ± 37.7	42.3 ± 37.7	4.20‡	–0.66 to 9.07	0.090
APROCCHSS (original)	42 ± 38	38 ± 38	N/A	N/A	0.05
Days alive and free of hospital					
ADRENAL (original)	40.0 ± 32.0	38.6 ± 32.4	1.45‡	–0.59 to 3.49	0.164
ADRENAL–Sepsis-3	36.3 ± 31.9	34.8 ± 32.6	1.68	–1.16 to 4.52	0.245
ADRENAL–APROCCHSS	31.6 ± 31.5	28.3 ± 31.1	3.67‡	–0.36 to 7.70	0.074
APROCCHSS (original)	31 ± 33	29 ± 33	N/A	N/A	0.27
Days alive and free of mechanical ventilation					
ADRENAL (original)	61.2 ± 35.6	59.1 ± 36.1	2.18‡	–0.11 to 4.46	0.062
ADRENAL–Sepsis-3	57.0 ± 37.2	53.7 ± 38.2	3.72‡	0.40 to 7.04	0.028
ADRENAL–APROCCHSS	48.5 ± 39.2	45.4 ± 39.1	3.78‡	–1.28 to 8.84	0.143
APROCCHSS (original)	45 ± 39	40 ± 39	N/A	N/A	0.04
Recurrence of mechanical ventilation					
ADRENAL (original)	180/1,842 (9.8)	154/1,850 (8.3)	1.18*	0.96 to 1.45	0.113
ADRENAL–Sepsis-3	93/967 (9.6%)	71/974 (7.3%)	1.36*	0.98 to 1.88	0.063
ADRENAL–APROCCHSS	38/455 (8.4%)	31/447 (6.9%)	1.22*	0.74 to 2.0	0.432
APROCCHSS (original)	N/A	N/A	N/A	N/A	N/A
Days alive and free of RRT					
ADRENAL (original)	42.6 ±39.1	40.4 ± 38.5	2.37‡	–2.00 to 6.75	0.294
ADRENAL–Sepsis-3	60.9 ± 38.2	57.2 ± 39.6	4.00‡	0.57 to 7.43	0.022
ADRENAL–APROCCHSS	51.5 ± 40.6	49.5 ± 40.9	2.54‡	–2.73 to 7.82	0.344
APROCCHSS (original)	N/A	N/A	N/A	N/A	N/A
Use of RRT					
ADRENAL (original)	567/1,853 (30.6)	609/1,860 (32.7)	0.94*	0.86 to 1.03	0.178
ADRENAL–Sepsis-3	350/969 (36.1%)	389/973 (40.0%)	0.83*	0.69 to 1.00	0.049
ADRENAL–APROCCHSS	239/454 (52.6%)	217/447 (48.5%)	1.16*	0.89 to 1.52	0.275
APROCCHSS (original)	N/A	N/A	N/A	N/A	N/A
New bacteremia or fungemia					
ADRENAL (original)	262/1,853 (14.1)	262/1,860 (14.1)	1.00*	0.86 to 1.16	0.957
ADRENAL–Sepsis-3	143/969 (14.8%)	135/972 (13.9%)	1.07*	0.82 to 1.39	0.616
ADRENAL–APROCCHSS	66/455 (14.5%)	60/448 (13.4%)	1.13*	0.75 to 1.70	0.560
APROCCHSS (original)	49/614 (8.0%)	48/626 (7.7%)	1.04	0.71 to 1.53	0.86
Blood transfusion					
ADRENAL (original)	683/1,848 (37.0)	773/1,855 (41.7)	0.82*	0.72 to 0.94	0.004
ADRENAL–Sepsis-3	393/973 (40.4%)	424/977 (43.4%)	0.89*	0.74 to 1.07	0.212
ADRENAL–APROCCHSS	224/455 (49.2%)	205/450 (45.6%)	1.17*	0.90 to 1.52	0.246
APROCCHSS (original)	N/A	N/A	N/A	N/A	N/A
180-day mortality					
ADRENAL (original)	571/1,812 (31.5%)	574/1,803 (31.8%)	0.99*	0.86 to 1.13	0.834
ADRENAL–Sepsis-3	349/959 (36.4%)	367/952 (38.6%)	0.89*	0.76 to 1.10	0.239
ADRENAL–APROCCHSS	199/448 (44.4%)	211/441 (47.8%)	0.84*	0.64 to 1.11	0.220
APROCCHSS (original)	285/611 (46.6%)	328/625 (52.5%)	0.89*	0.79 to 0.99	0.04

Plus–minus values represent means ± standard deviations. The proportions are presented as numbers of subjects/denominator (percentage). Median (IQR) values are presented for not normally distributed variables. The analysis of mortality at days 28 and 180 reported in this table, adjusted for stratification variables, is a logistic regression including treatment and admission type as fixed effects and study site as a random effect.

*Odds ratios; †Hazard ratios. ‡Mean absolute differences.

ADRENAL, Adjunctive Glucocorticoid Therapy in Patients with Septic Shock trial; APROCHSS, Activated Protein C and Corticosteroids for Human Septic Shock trial; ICU, intensive care unit; IQR, interquartile range; N/A, not available (value not reported in the main article or in the Supplemental Digital Content 1 [http://links.lww.com/ALN/C48] of the APROCCHSS publication and hence not available); RRT, renal replacement therapy; Sepsis-3, third international consensus definitions for sepsis and septic shock.

originating from *post hoc* analyses, and may be regarded as hypothesis-generating.

Limitations

The Sepsis-3 task force stipulated three criteria for the diagnosis of septic shock: MAP of less than 65 mmHg, lactate of more than 2 mmol/l, and absence of hypovolemia. Volume status is difficult to assess in critically ill patients. Baseline filling pressures assessed by the central venous pressure was within normal limits in the Sepsis-3 cohort, and this was used as a surrogate for euvolemia. Our study was limited to patients who required a minimum of 4 h of vasopressor therapy and mechanical ventilator support, neither of which are required to meet the Sepsis-3 criteria for septic shock. Therefore, the number of eligible patients who would have met Sepsis-3 criteria may have been underestimated. Because a number of patients who were deemed to be in danger of imminent death or in whom death was deemed inevitable during the admission were excluded (which were not exclusions in the original Sepsis-3 validation cohort), the mortality in our cohort of patients meeting Sepsis-3 criteria may have been underestimated. Matching of the ADRENAL trial participants with the APROCCHSS cohort may not have been precise, because there were different duration requirements for pressor therapy for entry into the study. The APROCCHSS trial used 6 h of pressor therapy, as opposed to only 4 h in the ADRENAL trial. However, this is mitigated by the baseline equivalence of patients between the ADRENAL–APROCCHSS and original APROCCHSS trials. Moreover, the analysis of primary outcome in the cohort of patients in the ADRENAL–APROCCHSS group who were randomized after 6 h did not reveal a treatment effect. Another key difference between the two trials was the exclusion of patients who had received etomidate, a known adrenal suppressant, in the ADRENAL trial. Although the impact of this exclusion criterion could not be evaluated in this analysis, it is well recognized that the use of etomidate was a significant confounder in the interpretation of the results of two earlier trials of low dose steroids in septic shock.[18,19] The absolute risk reduction of 3.6% in mortality in favor of hydrocortisone observed in the ADRENAL–APROCCHSS cohort may be considered as clinically significant, especially in the context of a safe and an inexpensive intervention, but the interpretation is limited by the lack of statistical significance, the *post hoc* nature of the analysis, and the reduced power due to the smaller sample size.

Conclusions

In the ADRENAL trial participants who fulfilled either the Sepsis-3 or the APROCCHSS inclusion criteria, a continuous infusion of hydrocortisone did not result in a significantly lower 90-day mortality than placebo in septic shock.

Research Support

Supported by National Health and Medical Research Council of Australia (Canberra, Australia) project grant Nos. 1004108 and 1124926 and Health Research Council of New Zealand (Auckland, New Zealand) project grant No. 12/206 to the ADRENAL study, which received indirect funding from the National Institute of Health Research (London, United Kingdom) after being adopted onto their research portfolio. Supported by a Practitioner Fellowship from Medical Research Future fund (Canberra, Australia; to Dr. Venkatesh) by Practitioner Fellowships from the National Health and Medical Research Council of Australia (to Drs. Bellomo, Finfer, and Myburgh).

Competing Interests

The authors declare no competing interests.

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