Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods:

Assessment of the validity of assumptions related to the timing of hydrocortisone to fludrocortisone initiation: We used the Medical Information Mart for Intensive Care (MIMIC-IV),[9] a single center electronic medical record based-dataset, to estimate the median time and interquartile range (IQR) from hydrocortisone to fludrocortisone initiation among patients with septic shock on norepinephrine who were given both treatments (n=53) to better understand the implications of our treatment assignment assumptions that fludrocortisone is given concurrent with, or shortly after hydrocortisone. In this analysis, the median time from hydrocortisone initiation to fludrocortisone initiation was 120 minutes (interquartile range [IQR] 0-840 minutes). Thus, most hydrocortisone was started before fludrocortisone and most fludrocortisone was started within 2 hours of hydrocortisone, although the upper quartile of 14 hours suggested that the use of a calendar day-based database may increase the risk for immortal time bias.

Missing Data: Missing data occurs in <0.01% of variable fields in the Premier Healthcare Database. No patients included in our study had missing data. For data fields related to diagnostic, procedure or charge codes, patients without specific codes used to identify a study variable/condition were interpreted as not having the variable/condition.

Patients with multiple episodes of septic shock: Among patients with septic shock present on admission who started, stopped, and then restarted norepinephrine later in the hospital course, only the first instance of norepinephrine per patients was evaluated. As part of the deidentification process for the Premier Healthcare Database, temporal information related to multiple hospitalizations is removed. Thus, individual hospitalizations were treated as individual patients.

Statistical analysis plan

Analyses were performed with R software, version 4.0.5 (R Foundation for Statistical Computing). Alpha was two-sided and set at 0.05 for the primary outcome TMLE analysis. We did not adjust for multiple comparisons; thus, all analyses other than the primary outcome should be viewed as hypothesis generating. The protocol for this study was previously deposited in an online repository.[10] This study was designated not Human Subjects Research by Boston University's Institutional Review Board (#H-41795). The design of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[11]

Covariate Balance: Covariables were summarized using means (SD), medians (IQR), and counts (%) as appropriate stratified by treatment assignment. Absolute standardized mean differences were used to compare covariables between treatment assignments.

Unadjusted outcomes: We reported the proportion of patients for each treatment assignment and the unadjusted risk differences (95% confidence intervals [CIs]) for dichotomous outcomes and the mean values for each treatment assignment and mean differences (95% CI) for continuous outcomes. Unadjusted survival curves were constructed using the Kaplan-Meier estimator[12] for the primary outcome of hospital death or discharge to hospice.

Adjusted outcomes: We used targeted maximum likelihood estimation (TMLE)[13] to calculate adjusted risk differences (95% CI) and mean differences (95% CI). TMLE is a doubly robust

method that provides semiparametric, locally efficient substitution estimators that are valid estimates of the treatment effect when models estimating the probability of treatment assignment or the probability of the outcome are correctly specified. TMLE is a three-step process[14]: (1) outcome mechanism (i.e., outcome model) used to generate the predicted outcome under both exposure levels; (2) exposure mechanism (i.e., exposure/propensity score model) used to update the initial estimator and optimize the bias-variance tradeoff; (3) calculate the average treatment effect in targeted predicted outcome pairs. We used an ensemble machine learner (Super Learner[15,16]) to create the outcome and exposure/propensity score models. Ensemble machine learners use multiple modeling algorithms and have multiple advantages over conventional generalized linear models including flexible handling of variable interactions and non-linear variables, and high predictive accuracy. Our Super Learner library included logistic regression (generalized linear models with a logit link using R's glm function), random forests (using the ranger package), and LASSO models (using the glmnet package) and generalized additive models (using the gam package). The same variables were used to both model the treatment mechanism and the outcome model via Super Learner, and these variables encompassed all covariates. Covariates were defined *a priori* except for insurance status, pneumonia present on admission, etomidate use, renal replacement therapy, time from norepinephrine to hydrocortisone initiation, surgical care unit, and admission hospital which were added as a result of reviewer feedback. Accuracy was assessed using an empirical estimate of AUC for the treatment mechanism model and a cross-validated estimate of pseudo R squared for the outcome model. Propensity scores were truncated (lower bound = 5/sqrt(n)/log(n), upper bound = 1 - 5/sqrt(n)/log(n)) to avoid near positivity assumption violations.

Sensitivity analyses: We calculated an E-value for the primary outcome to estimate the strength of association (on the risk ratio scale) between unmeasured confounders, treatment assignment, and the primary outcome that would be needed to bring the association between treatment assignment and the primary outcome to zero.[17,18] A negative control analysis was used to assess the risk of residual confounding.[19] For the negative control analysis we evaluated an outcome (blood transfusion after study day 0) not expected to differ based on use of fludrocortisone therapy, and not expected to be in the causal pathway between corticosteroid selection and reductions in shock severity and mortality, but which is frequently required during critical illness and associated with disease severity.[20] To minimize potential effects of the Coronavirus 2019 pandemic on results we repeated our analyses after excluding patients discharged in 2020. To minimize the potential for immortal time bias, we repeated our analyses limiting to patients who met all inclusion criteria on the day of hospital admission (i.e., hospital day 1). To assess the robustness of results to possible covariate misclassification (covariates that occurred on the same day as treatment assignment were assumed to occur prior to treatment assignment in the primary analysis; however, given the Premier Healthcare Database has granularity to the level of calendar day, it is possible that some covariates occurred after treatment assignment), we repeated analyses among patients who met inclusion criteria on hospital day 2 or 3 and classified covariates using variables from the day prior to treatment assignment.

Difference-in-differences sensitivity analysis: To further explore the robustness of findings to potential residual confounding by indication, secular changes in sepsis treatment, and patient illness severity, we used the difference-in-differences method[21] that compared changes in outcomes before and after hospital-level adoption of fludrocortisone following the March 2018

publication of the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial[22] – the largest clinical trial showing mortality benefit of combination hydrocortisone- fludrocortisone compared to placebo. To identify hospitals that adopted and did not adopt fludrocortisone after APROCCHSS, we calculated the change in the proportion of patients in each hospital that received hydrocortisone-fludrocortisone in the years just before (2017) and after (2019) APROCCHSS publication. We then assigned hospitals with a change in fludrocortisone initiation in the top quartile of hospitals as "adopter" hospitals and hospitals in the bottom quartile as "non-adopter" (control) hospitals. Hospitals with caseloads less than 10 patients in either year were excluded. Then, we assigned each patient as either admitted to an "adopter" or "non-adopter" hospital during the pre-APROCCHSS (discharged between 2016-2017) or post-APROCCHSS (discharged between 2019-2020) time periods. We used hierarchical linear probability models (admission hospital as a random intercept) including terms for hospital discharge pre- or post-APROCCHSS, admission to an "adopter" or "non-adopter" hospital, and an interaction term, to quantify the difference in the probability of hospital death or discharge to hospice between patients admitted to hospitals after fludrocortisone adoption and patients admitted to control hospitals. Note that the difference-in-differences analysis answers a question related to hospital adoption of fludrocortisone, not individual patient-level receipt of fludrocortisone. We tested for the presence of significant interaction between study quarter and treatment arm to assess pre-APROCCHSS parallel trends. We used blood transfusion after study day 0 as a falsification test negative control outcome in the difference-in-differences analysis.

eTable 1: Comparison between target trial and the observational study of the effectiveness of fludrocortisone added to hydrocortisone versus hydrocortisone alone in patients with septic shock.[1]

Approach	Target Trial	Observational study
Eligibility criteria	Hospitalized patients ≥18 years of age who are within 3 days of hospitalization, who have a diagnosis of septic shock and are receiving norepinephrine, do not receive fludrocortisone as an outpatient, and who were initiated on hydrocortisone within the same calendar day.	Same as for the target trial except that pre-hospitalization medications are unknown. Thus, patients with diagnoses that could suggest an alternative indication for fludrocortisone were additionally excluded
Treatment strategies	Initiation of fludrocortisone to hydrocortisone versus usual care	Same as for target trial
Treatment assignment	Individual-level randomization without blinding	Based on observed data assignment
Outcomes	Primary: Hospital death or discharge to hospice Secondary: hospital death, vasopressor-free days by day 28, hospital-free days by day 28	Same as for target trial
Follow-up	From treatment assignment until hospital discharge	Same as for target trial
Causal estimand	Intention-to-treat and per-protocol (as-assigned) effects	Intention-to-treat effect

[1]Table design adapted from Hernán MA, NEJM 2021[1]

eTable 2: Study eligibility criteria

Criteria	Definition
Discharge date range	Included patients with hospital discharge months that occurred during the years 2016-2020
Septic shock on admission and receiving norepinephrine	ICD-10 code R65.21 ('explicit septic shock) that was labeled as POA or as admitting diagnosis AND charge code for norepinephrine within the first 3 calendar days of hospital admission
Started on hydrocortisone between hospital days 1-3 (hospital day 1 represents the first calendar day of hospitalization)	Charge codes for parenteral hydrocortisone succinate or phosphate on a calendar day in which norepinephrine was also charged and within the first 3 calendar days of hospital admission. The day of hydrocortisone initiation was assigned study day 0.
Adults	Age greater than or equal to 18
No alternative indications for fludrocortisone: Adrenal insufficiency, orthostatic hypotension, or congenital adrenal hyperplasia POA	Excluded patients with the following ICD-10 diagnosis codes that were labeled as POA: "E27.1", "E27.2", "E27.3", "E27.40", "E27.49", "E25.0", "I95.1"

POA: present on admission

eTable 3: Study variable definitions

Study variable	Definition
Treatment assignments	
Hydrocortisone-fludrocortisone	Charge codes for fludrocortisone on the same calendar day that hydrocortisone was initiated
Hydrocortisone alone	No charge codes for fludrocortisone on the same calendar day that hydrocortisone was initiated
Outcomes	
Composite of hospital death or discharge to hospice (primary)	DISC_STATUS variable set to 20 (hospital death), 50 (discharged to hospice – home), or 51 (discharged to hospice – medical facility)
Hospital death (secondary)	DISC_STATUS variable set to 20 (hospital death)
Vasopressor-free days by day 28 (secondary)	The number of calendar days with a charge for norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine from study day 0 minus 28. Patients who died in the hospital of had 28 or more days of vasopressors were assigned a score of 0.
Hospital-free days by day 28 (secondary)	The number of calendar days from study 0 to hospital discharged minus 28. Patients who died in the hospital or had lengths of stay of 28 or more days were assigned a score of 0.
Potential complications	
Hypernatremia that was not POA	ICD-10 diagnosis code for hypernatremia ("E87.0") not labeled as POA
Hospital-associated infection that was not POA	ICD-10 diagnosis codes for ventilator-associated pneumonia, central-line associated infections, urinary catheter associated infection, or surgical site infection ("T80.211A", "T80.211D", "T80.211S", "T83.511A", "T83.511D", "T83.511S", "J95.851", "T81.4x") that were not labeled as POA
Covariates	
Age	Dataset variable
Female sex	Dataset variable
Health insurance type	Dataset variable collapsed into categories of medicare, Medicaid, commercial, self-pay, and other.
Discharge season/year	Dataset variable
Elixhauser comorbidity score POA	ICD-10 diagnosis codes labeled as POA then inputted into R comorbidity package to extract "score" variable output[2–4]
CHF POA[2–4]	Elixhauser score component (chf output variable)
Connective tissue disease POA	Elixhauser score component (rheumd output variable)[2–4]
Pneumonia POA	ICD-10 diagnosis codes "J09x", "J10x", "J11x", "J12x", "J13x", "J14x", "J15x", "J16x", "J17x", "J18x", "J85x", or "J86x" labeled as POA
Major surgery per HCUP between days 0-2 of hospital admission and on or before the day of hydrocortisone initiation	ICD-10 PCS codes categorized as HCUP major surgery[5] (diagnostic or therapeutic) on or before study day 0 (day of hydrocortisone initiation)
Acute organ dysfunctions POA (Angus)	ICD-10 diagnosis codes labeled as POA using previously published ICD-9 to ICD-10 conversions for "Angus" organ dysfunctions[6,7]
Days from hospital admission to hydrocortisone initiation	Days from hospital admission to hydrocortisone initiation
Days from norepinephrine initiation to hydrocortisone initiation	Days from norepinephrine initiation to hydrocortisone initiation
Volume of resuscitative fluids on the day of hydrocortisone initiation	Charge codes for balanced (lactated ringers, Normosol-R, Plasmalyte 148/Plasmalyte A) or unbalanced (normal saline) intravenous fluid with a volume of 500 ml or 1000 ml). Total daily volume calculated by taking the product between fluid bag volume and the number of charges on study day 0

Enteral medication administration on the day of hydrocortisone initiation	Charge codes on study day 0 under the pharmacy department heading listed as "ORAL" and not "FLUDROCORTISONE"
Use of etomidate on or before the day of hydrocortisone initiation	Charge codes on or before study day 0 under the pharmacy department heading listed as “ETOMIDATE PARENTERAL”
Use of renal replacement therapy on or before the day of hydrocortisone initiation	IC-10 Procedure codes of "5A1D70Z", "5A1D80Z", "5A1D00Z", "5A1D60Z", or "5A1D90Z" on or before study day 0
Serum cortisol measured on the day of hydrocortisone initiation	Charge codes on study day 0 for random, free, am, or pm serum cortisol
Cosyntropin administered on the day of hydrocortisone initiation	Charge on study day 0 for the medication cosyntropin
Vasopressor use on the day of hydrocortisone initiation	
Dopamine	Charge code for dopamine on study day 0
Epinephrine	Charge code for epinephrine on study day 0
Phenylephrine	Charge code for phenylephrine on study day 0
Vasopressin	Charge code for vasopressin on study day 0
Invasive mechanical ventilation on the day of hydrocortisone initiation	Charge code[8] for invasive mechanical ventilation on study day 0
Admission hospital	Dataset variable
US Census Region	Dataset variable
Teaching hospital status	Dataset variable
Hospital bed number	Dataset variable
Hospital case load	Number of included study patients per hospital
Surgical care unit	Charge codes on or before study day 0 where STD_CHG_DESC variable was any of the following: "R&B SICU (SURGICAL ICU) ISOLATION", "R&B SICU (SURGICAL ICU)", "R&B BURN ICU", "R&B TRAUMA ICU", "R&B STEP DOWN SICU (SURGICAL ICU) SEMI PRIVATE", "R&B STEP DOWN SICU (SURGICAL ICU) ISOLATION", "R&B STEP DOWN SICU (SURGICAL ICU) PRIVATE", "R&B STEP DOWN SICU (SURGICAL ICU) DELUXE", "R&B TRANSPLANT ICU", "R&B CVICU", "R&B CVICU ISOLATION", "R&B STEP DOWN CVICU SEMI PRIVATE", "R&B STEP DOWN CVICU ISOLATION", "R&B STEP DOWN CVICU PRIVATE", "R&B STEP DOWN CVICU DELUXE"

CHF: congestive heart failure; HCUP: healthcare cost and utilization project; ICD-10: international classification of diseases, tenth revision; N/A: not applicable; PCS: procedure coding system; POA: present on admission; SOFA: sequential organ failure assessment score; US: United States

eTable 4: Baseline covariates in the sensitivity analysis cohort excluding patients discharged in 2020

Variable	Hydrocortisone (n=68,549)	Hydrocortisone and Fludrocortisone (n=1,519)	Absolute standardized mean difference
Age, years median (IQR)	67 (57-76)	64 (54-74)	0.19
Sex, No. (%)			0.07
Female	33,821 (49.3)	696 (45.8)	
Male	34,728 (50.7)	823 (54.2)	
Health insurance type, No. (%)			0.14
Commercial	10,015 (14.6)	218 (14.4)	
Medicaid	9,370 (13.7)	268 (17.6)	
Medicare	45,259 (66.0)	935 (61.6)	
Self-pay	2,154 (3.1)	67 (4.4)	
Other	1,751 (2.6)	31 (2.0)	
Elixhauser comorbidity score POA, median (IQR)	6 (4-7)	6 (4-7)	0.03
CHF POA, No. (%)	24,899 (36.3)	565 (37.2)	0.02
Connective tissue disease POA, No. (%)	5,264 (7.7)	82 (5.4)	0.09
Pneumonia POA, No. (%)	25,327 (36.9)	584 (38.4)	0.03
Major surgery per HCUP on or before day of corticosteroid initiation, No. (%)	6,748 (9.8)	93 (6.1)	0.14
Acute organ dysfunction, No. (%)			
Respiratory	28,953 (42.2)	729 (48.0)	0.12
Hematologic	20,738 (30.3)	494 (32.5)	0.05
Hepatic	8,493 (12.4)	201 (13.2)	0.03
Renal	47,806 (69.7)	1,068 (70.3)	0.01
Time from hospital admission to corticosteroid treatment, No. (%)			0.12
0 days	36,665 (53.5)	725 (47.7)	
1 day	25,901 (37.8)	663 (43.6)	
2 days	5,983 (8.7)	131 (8.6)	
Time from norepinephrine initiation to hydrocortisone treatment, No. (%)			0.14
0 days	48,334 (70.5)	984 (64.8)	
1 day	17,668 (25.8)	489 (32.2)	
2 days	2,547 (3.7)	46 (3.0)	
Volume of resuscitative fluids on the day of corticosteroid initiation, ml median (IQR)	2,000 (0-4,500)	2,500 (0-5,000)	0.12
Enteral medication administration other than fludrocortisone on day of corticosteroid initiation, No. (%)	41,476 (60.5)	1,259 (82.9)	0.51
Serum cortisol measured on the day of corticosteroid initiation, No. (%)	11,676 (17.0)	222 (14.6)	0.07
Cosyntropin administered on the day of corticosteroid initiation, No. (%)	343 (0.5)	4 (0.3)	0.04
Etomidate use on or before the day of hydrocortisone initiation, No. (%)	17,903 (26.1)	461 (30.3)	0.09
Renal replacement therapy on or before the day of hydrocortisone initiation, No. (%)	5,547 (8.1)	136 (9.0)	0.03
Vasopressor use on the day of corticosteroid initiation, No. (%)		2,604	
Dopamine	4,909 (7.2)	64 (4.2)	0.13

Epinephrine	14,108 (20.6)	320 (21.1)	0.01
Phenylephrine	16,837 (24.6)	368 (24.2)	0.01
Vasopressin	35,123 (51.2)	1,002 (66.0)	0.30
Vasopressor count on the day of corticosteroid initiation, median (IQR)	2 (1-3)	2 (1-3)	0.12
Invasive mechanical ventilation on the day of corticosteroid initiation, No. (%)	40,602 (59.2)	985 (64.8)	0.12
US Census Region, No. (%)			0.15
Midwest	14,531 (21.2)	289 (19.0)	
Northeast	8,834 (12.9)	254 (16.7)	
South	31,764 (46.3)	631 (41.5)	
West	13,420 (19.6)	345 (22.7)	
Teaching hospital status, No. (%)	35,066 (51.2)	1,061 (69.8)	0.39
Hospital bed number, No. (%)			0.28
0-99	2,284 (3.3)	43 (2.8)	
100-199	9,009 (13.1)	132 (8.7)	
200-299	11,640 (17.0)	179 (11.8)	
300-399	11,299 (16.5)	204 (13.4)	
400-499	8,686 (12.7)	209 (13.8)	
500+	25,631 (37.4)	752 (49.5)	
Hospital case load, median (IQR)	232 (119-392)	363 (176-503)	0.39
Surgical care unit, No. (%)	2,604 (3.8)	91 (6.0)	0.10
Discharge quarter/year, No. (%)			1.10
1/2016	3,709 (5.4)	10 (0.7)	
2/2016	3,435 (5.0)	8 (0.5)	
3/2016	3,363 (4.9)	13 (0.9)	
4/2016	3,673 (5.4)	16 (1.1)	
1/2017	4,336 (6.3)	13 (0.9)	
2/2017	4,198 (6.1)	9 (0.6)	
3/2017	3,967 (5.8)	10 (0.7)	
4/2017	4,340 (6.3)	15 (1.0)	
1/2018	4,929 (7.2)	35 (2.3)	
2/2018	4,297 (6.3)	233 (15.3)	
3/2018	4,212 (6.1)	191 (12.6)	
4/2018	4,659 (6.8)	189 (12.4)	
1/2019	5,204 (7.6)	237 (15.6)	
2/2019	4,786 (7.0)	194 (12.8)	
3/2019	4,525 (6.6)	182 (12.0)	
4/2019	4,916 (7.2)	164 (10.8)	
1/2020	2,783 (6.1)	102 (9.7)	
2/2020	2,071 (4.5)	83 (7.9)	
3/2020	2,073 (4.5)	78 (7.4)	
4/2020	2,243 (4.9)	64 (6.1)	

IQR: interquartile range; POA: present on admission; US: United States

eTable 5: Baseline covariates in the sensitivity analysis cohort limited to patients who met inclusion criteria on hospital day 1

Variable	Hydrocortisone (n=45,835)	Hydrocortisone and Fludrocortisone (n=1,052)	Absolute standardized mean difference
Age, years median (IQR)	67 (57-76)	64 (52-73)	0.22
Sex, No. (%)			0.06
Female	22,476 (49.0)	483 (45.9)	
Male	23,359 (51.0)	569 (54.1)	
Health insurance type, No. (%)			0.15
Commercial	6,673 (14.6)	153 (14.5)	
Medicaid	6,165 (13.5)	194 (18.4)	
Medicare	30,446 (66.4)	646 (61.4)	
Self-pay	1,338 (2.9)	36 (3.4)	
Other	1,213 (2.6)	23 (2.2)	
Elixhauser comorbidity score POA, median (IQR)	6 (4-7)	6 (4-7)	0.06
CHF POA, No. (%)	16,494 (36.0)	385 (36.6)	0.01
Connective tissue disease POA, No. (%)	4,092 (8.9)	69 (6.6)	0.09
Pneumonia POA, No. (%)	17,451 (38.1)	389 (37.0)	0.02
Major surgery per HCUP on or before day of corticosteroid initiation, No. (%)	3163 (6.9)	45 (4.3)	0.11
Acute organ dysfunction, No. (%)			
Respiratory	21,324 (46.5)	570 (54.2)	0.15
Hematologic	13,382 (29.2)	322 (30.6)	0.03
Hepatic	5,720 (12.5)	143 (13.6)	0.03
Renal	32,221 (70.3)	751 (71.4)	0.02
Volume of resuscitative fluids on the day of corticosteroid initiation, ml median (IQR)	2,500 (0-5,000)	3,500 (1,000-6,000)	0.23
Enteral medication administration other than fludrocortisone on day of corticosteroid initiation, No. (%)	25,149 (54.9)	843 (80.1)	0.56
Serum cortisol measured on the day of corticosteroid initiation, No. (%)	7,863 (17.2)	175 (16.6)	0.01
Cosyntropin administered on the day of corticosteroid initiation, No. (%)	141 (0.3)	2 (0.2)	0.02
Etomidate use on or before the day of hydrocortisone initiation, No. (%)	10,505 (22.9)	275 (26.1)	0.08
Renal replacement therapy on or before the day of hydrocortisone initiation, No. (%)	2,363 (5.2)	62 (5.9)	0.03
Vasopressor use on the day of corticosteroid initiation, No. (%)			
Dopamine	3,373 (7.4)	39 (3.7)	0.16
Epinephrine	9,857 (21.5)	232 (22.1)	0.01
Phenylephrine	10,696 (23.3)	262 (24.9)	0.04
Vasopressin	22,501 (49.1)	690 (65.6)	0.34
Vasopressor count on the day of corticosteroid initiation, median (IQR)	2 (1-3)	2 (1-3)	0.15
Invasive mechanical ventilation on the day of corticosteroid initiation, No. (%)	25,327 (55.3)	643 (61.1)	0.12
US Census Region, No. (%)			0.15
Midwest	10,186 (22.2)	247 (23.5)	

Northeast	6,001 (13.1)	157 (14.9)	
South	20,739 (45.2)	402 (38.2)	
West	8,909 (19.4)	246 (23.4)	
Teaching hospital status, No. (%)	23,444 (51.1)	767 (72.9)	0.46
Hospital bed number, No. (%)			0.31
0-99	1,599 (3.5)	33 (3.1)	
100-199	6,175 (13.5)	80 (7.6)	
200-299	7,955 (17.4)	146 (13.9)	
300-399	7,599 (16.6)	126 (12.0)	
400-499	5,644 (12.3)	152 (14.4)	
500+	16,863 (36.8)	515 (49.0)	
Hospital case load, median (IQR)	229 (117-392)	370 (183-503)	0.45
Surgical care unit, No. (%)	1,583 (3.5)	68 (6.5)	0.14
Discharge quarter/year, No. (%)			0.92
1/2016	1,919 (4.2)	9 (0.9)	
2/2016	1,805 (3.9)	5 (0.5)	
3/2016	1,775 (3.9)	5 (0.5)	
4/2016	2,006 (4.4)	13 (1.2)	
1/2017	2,270 (5.0)	5 (0.5)	
2/2017	2,256 (4.9)	3 (0.3)	
3/2017	2,131 (4.6)	3 (0.3)	
4/2017	2,248 (4.9)	12 (1.1)	
1/2018	2,668 (5.8)	13 (1.2)	
2/2018	2,334 (5.1)	116 (11.0)	
3/2018	2,238 (4.9)	88 (8.4)	
4/2018	2,456 (5.4)	83 (7.9)	
1/2019	2,847 (6.2)	96 (9.1)	
2/2019	2,632 (5.7)	92 (8.7)	
3/2019	2,414 (5.3)	101 (9.6)	
4/2019	2,666 (5.8)	81 (7.7)	

IQR: interquartile range; POA: present on admission; US: United States

eTable 6: Baseline covariates in the sensitivity analysis cohort limited to patients who met inclusion criteria on hospital days 2 or 3 and covariates were defined on the day before treatment assignment

Variable	Hydrocortisone (n=40,160)	Hydrocortisone and Fludrocortisone (n=1,228)	Absolute standardized mean difference
Age, years median (IQR)	66 (57-76)	64 (55-73)	0.18
Sex, No. (%)			0.07
Female	19,660 (49.0)	558 (45.4)	
Male	20,500 (51.0)	670 (54.6)	
Health insurance type, No. (%)			0.14
Commercial	5,806 (14.5)	165 (13.4)	
Medicaid	5,835 (14.5)	233 (19.0)	
Medicare	26,105 (65.0)	743 (60.5)	
Self-pay	1,354 (3.4)	58 (4.7)	
Other	1,060 (2.6)	29 (2.4)	
Elixhauser comorbidity score POA, median (IQR)	6 (4-8)	6 (4-7.25)	0.04
CHF POA, No. (%)	15,169 (37.8)	463 (37.7)	0.01
Connective tissue disease POA, No. (%)	2,369 (5.9)	48 (3.9)	0.09
Pneumonia POA, No. (%)	14,855 (37.0)	510 (41.5)	0.09
Major surgery per HCUP on or before day of corticosteroid initiation, No. (%)	3,075 (7.7)	60 (4.9)	0.11
Acute organ dysfunction, No. (%)			
Respiratory	15,194 (37.8)	553 (45.0)	0.15
Hematologic	12,743 (31.7)	402 (32.7)	0.02
Hepatic	5,186 (12.9)	148 (12.1)	0.03
Renal	28,195 (70.2)	870 (70.8)	0.01
Time from hospital admission to corticosteroid treatment, No. (%)			0.07
1 day	32,576 (81.1)	1,029 (83.8)	
2 days	7,584 (18.9)	199 (16.2)	
Time from norepinephrine initiation to hydrocortisone treatment, No. (%)			0.15
0 days	14,427 (35.9)	382 (31.1)	
1 day	22,431 (55.9)	771 (62.8)	
2 days	3,302 (8.2)	75 (6.1)	
Volume of resuscitative fluids on the day of corticosteroid initiation, ml median (IQR)	1,500 (0-3,500)	2,000 (0-4,000)	0.14
Enteral medication administration other than fludrocortisone on day of corticosteroid initiation, No. (%)	19,626 (48.9)	665 (54.2)	0.11
Serum cortisol measured on the day of corticosteroid initiation, No. (%)	3,336 (8.3)	95 (7.7)	0.02
Cosyntropin administered on the day of corticosteroid initiation, No. (%)	104 (0.3)	3 (0.2)	0.00
Etomidate use on or before the day of hydrocortisone initiation, No. (%)	6,159 (15.3)	241 (19.6)	0.11
Renal replacement therapy on or before the day of hydrocortisone initiation, No. (%)	1,118 (2.8)	30 (2.4)	0.02
Vasopressor use on the day of corticosteroid initiation, No. (%)			

Dopamine	1,543 (3.8)	28 (2.3)	0.09
Epinephrine	3,508 (8.7)	107 (8.7)	0.00
Phenylephrine	5,560 (13.8)	161 (13.1)	0.02
Vasopressin	8,886 (22.1)	337 (27.4)	0.12
Vasopressor count on the day of corticosteroid initiation, median (IQR)	1 (1-2)	1 (1-2)	0.04
Invasive mechanical ventilation on the day of corticosteroid initiation, No. (%)	17,249 (43.0)	625 (50.9)	0.16
US Census Region, No. (%)			0.21
Midwest	8,362 (20.8)	233 (19.0)	
Northeast	4,953 (12.3)	231 (18.8)	
South	19,084 (47.5)	495 (40.3)	
West	7,761 (19.3)	269 (21.9)	
Teaching hospital status, No. (%)	20,903 (52.0)	873 (71.1)	0.40
Hospital bed number, No. (%)			0.27
0-99	1,313 (3.3)	29 (2.4)	
100-199	5,111 (12.7)	97 (7.9)	
200-299	6,594 (16.4)	165 (13.4)	
300-399	6,600 (16.4)	154 (12.5)	
400-499	5,148 (12.8)	190 (15.5)	
500+	15,394 (38.3)	593 (48.3)	
Hospital case load, median (IQR)	242 (124-397)	370 (206-503)	0.39
Surgical care unit, No. (%)	957 (2.4)	66 (5.4)	0.16
Discharge quarter/year, No. (%)			1.00
1/2016	1,790 (4.5)	1 (0.1)	
2/2016	1,630 (4.1)	3 (0.2)	
3/2016	1,588 (4.0)	8 (0.7)	
4/2016	1,667 (4.2)	3 (0.2)	
1/2017	2,066 (5.1)	8 (0.7)	
2/2017	1,942 (4.8)	6 (0.5)	
3/2017	1,836 (4.6)	7 (0.6)	
4/2017	2,092 (5.2)	3 (0.2)	
1/2018	2,261 (5.6)	22 (1.8)	
2/2018	1,963 (4.9)	117 (9.5)	
3/2018	1,974 (4.9)	103 (8.4)	
4/2018	2,203 (5.5)	106 (8.6)	
1/2019	2,357 (5.9)	141 (11.5)	
2/2019	2,154 (5.4)	102 (8.3)	
3/2019	2,111 (5.3)	81 (6.6)	
4/2019	2,250 (5.6)	83 (6.8)	
1/2020	2,295 (5.7)	122 (9.9)	
2/2020	2,045 (5.1)	118 (9.6)	
3/2020	1,927 (4.8)	102 (8.3)	
4/2020	2,009 (5.0)	92 (7.5)	

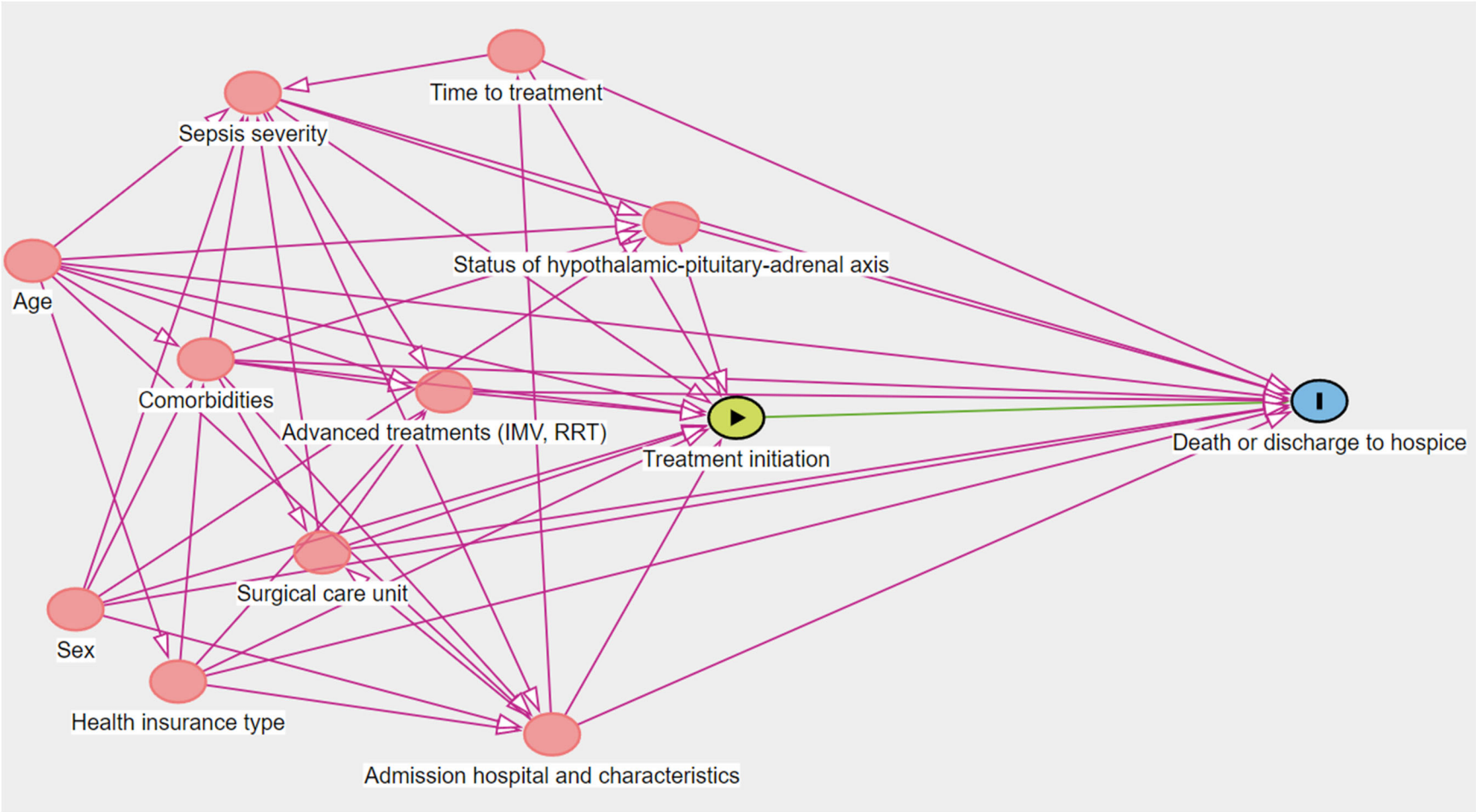
IQR: interquartile range; POA: present on admission; US: United States

eTable 7: Subgroup-analyses for the adjusted risk difference of hospital death or hospice discharge

Subgroup	Hydrocortisone alone	Hydrocortisone and fludrocortisone	Adjusted risk difference (95% CI)[a]
Age	No. patients with events/total no. of patients (%)		
<65 years	16,904/37,673 (44.9)	492/1,177 (41.8)	-3.5 (-3.9, -3.1)
≥65 years	26,765/48,322 (55.4)	584/1,103 (52.9)	-3.5 (-3.9, -3.1)
Sex			
Female	21,116/42,136 (51.1)	477/1,041 (45.9)	-3.8 (-4.1, -3.4)
Not female	22,553/43,859 (51.4)	599/1,239 (48.3)	-2.7 (-3.1, -2.3)
History of congestive heart failure			
Yes	16,282/31,663 (51.4)	402/848 (47.4)	-3.2 (-3.6, -2.8)
No	27,387/54,332 (51.4)	674/1,432 (41.7)	-1.9 (-2.3, -1.5)
Hospital admission to corticosteroid initiation			
<1 day	22,303/45,835 (48.7)	452/1,052 (43.0)	-4.6 (-4.9, -4.3)
≥1 day	17,024/32,576 (52.3)	515/1,029 (50.0)	-2.1 (-2.4, -1.8)

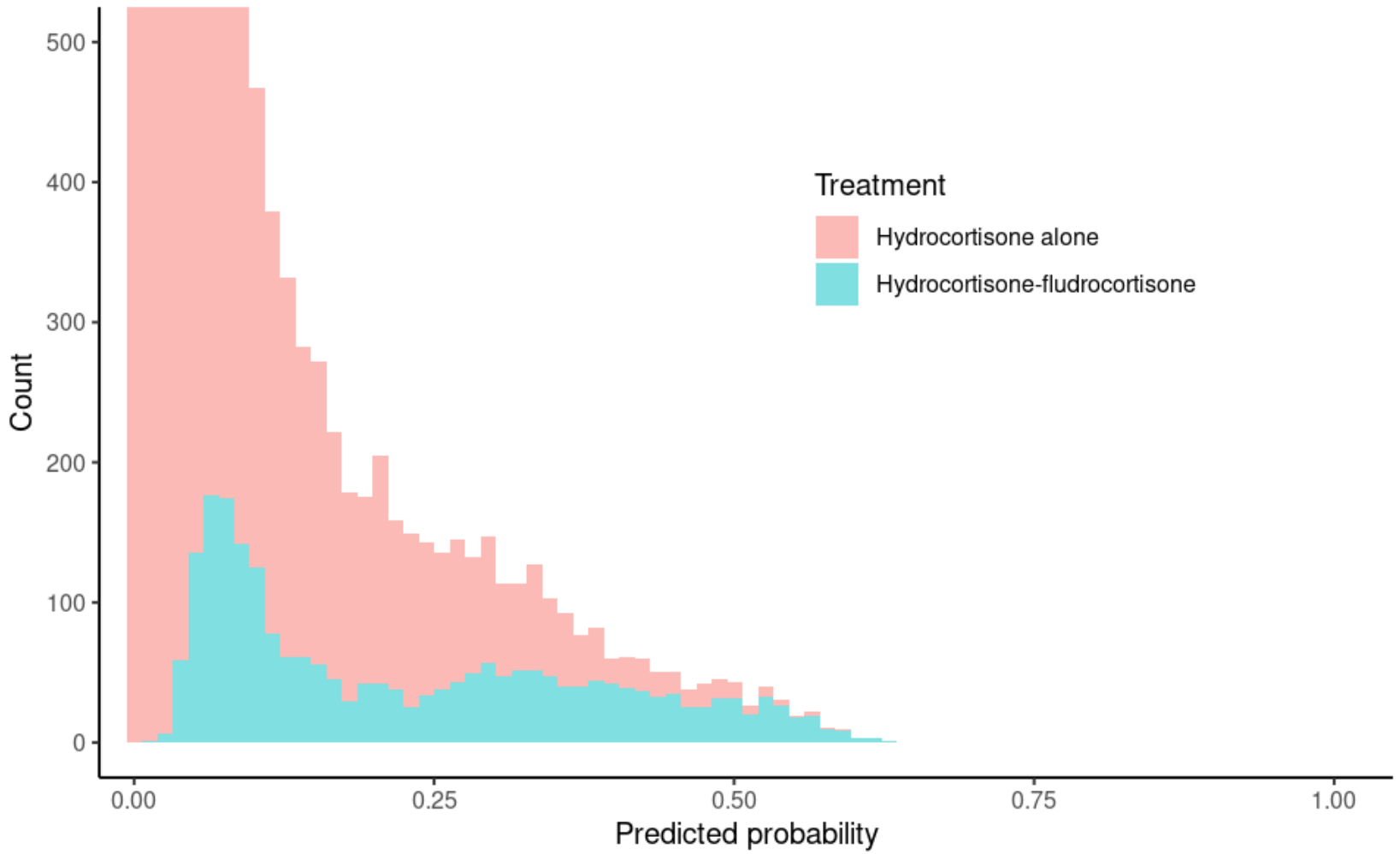
[a]Included covariates in subgroup analyses were limited to those selected *a priori*

eFigure 1: Directed acyclic graph



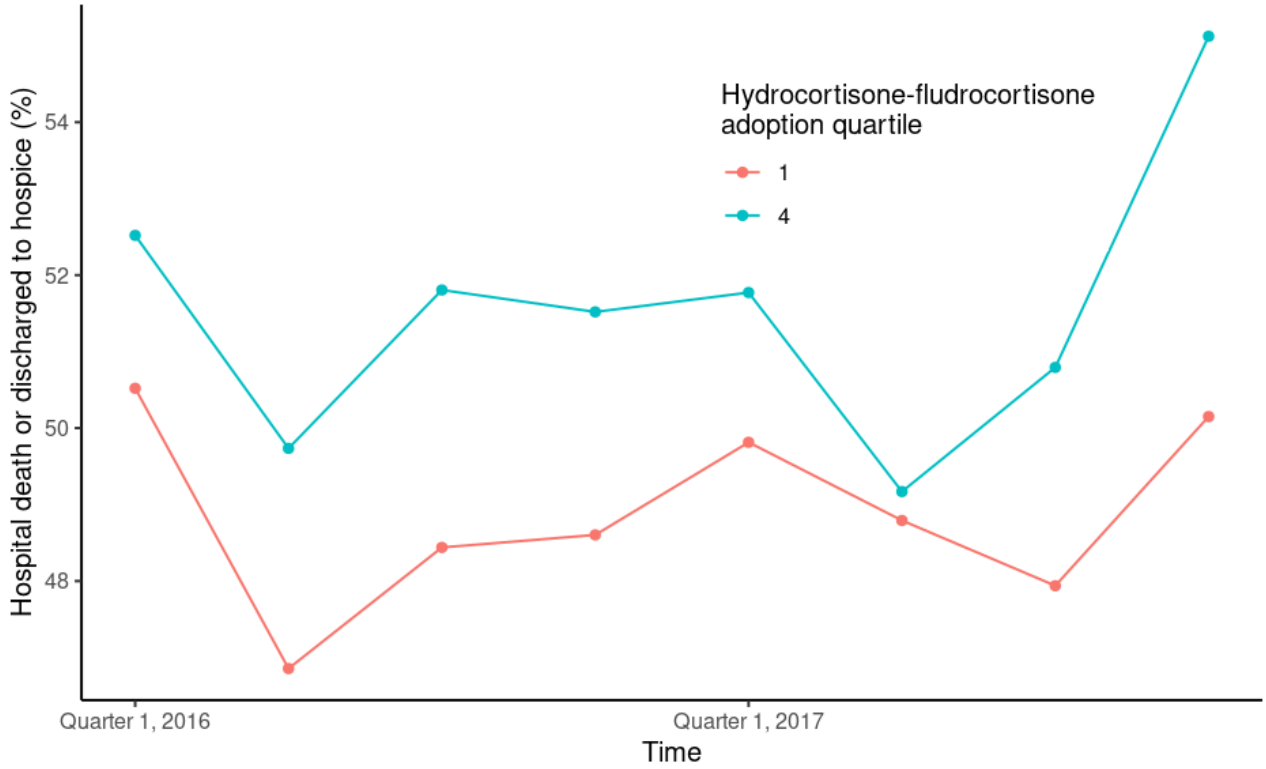
Shown are the proposed causal relationships between confounders, treatment assignment, and outcome. Arrows (red for relationships with confounding variables, green for the treatment effect that is the causal relationship of interest) show the direction of causal effects.

eFigure 2: Distribution of propensity scores



Shown are the propensity score (predicted probabilities of treatment with combination hydrocortisone-fludrocortisone) distributions stratified by observed treatment assignment for the primary analysis. The y-axis has been limited to counts below 500 to facilitate visualization. Propensity scores were truncated at 0.002 and 0.998, respectively based on the following formulae: lower bound = 5/sqrt(n)/log(n), upper bound = 1 - 5/sqrt(n)/log(n)). The Empirical Area Under the Receiver Operating curve (AUC) for the propensity score model was 0.97. The cross-validated pseudo-R squared for the primary outcome model was 0.15.

eFigure 3: Trends in hospital death or discharge hospice among patients with septic shock on norepinephrine and hydrocortisone from 2016-2017.



Shown are the percentage of patients per quarter that died in the hospital or were discharged to hospice from 2016 to 2017 prior to publication of the Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) clinical trial. Blue lines show outcome rates for patients admitted to hospitals that were in the top quartile ("adopter hospitals") of hydrocortisone-fludrocortisone adoption after APROCCHSS. Red lines show outcome rates for patients admitted to hospitals that were in the bottom quartile (control hospitals) of hydrocortisone-fludrocortisone adoption after APROCCHSS.

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