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RESEARCH ARTICLE

Hydrocortisone versus vasopressin for the management of adult patients with septic shock refractory to norepinephrine: A multicenter retrospective study

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Abstract

Study Objective: Significant practice variation exists when selecting between hydrocortisone and vasopressin as second line agents in patients with septic shock in need of escalating doses of norepinephrine. The goal of this study was to assess differences in clinical outcomes between these two agents.

Design: Multicenter, retrospective, observational study.

Setting: Ten Ascension Health hospitals.

Patients: Adult patients with presumed septic shock receiving norepinephrine prior to study drug initiation between December 2015 and August 2021.

Intervention: Vasopressin (0.03–0.04 units/min) or hydrocortisone (200–300 mg/day).

Measurements and Main Results: A total of 768 patients were included with a median (interquartile range) SOFA score of 10 (8–13), norepinephrine dose of 0.3 mcg/kg/min (0.1–0.5 mcg/kg/min), and lactate of 3.8 mmol/L (2.4–7.0 mmol/L) at initiation of the study drug. A significant difference in 28-day mortality was noted favoring hydrocortisone as an adjunct to norepinephrine after controlling for potential confounding factors (OR 0.46 [95% CI, 0.32–0.66]); similar results were seen following propensity score matching. Compared to vasopressin, hydrocortisone initiation was also associated with a higher rate of hemodynamic responsiveness (91.9% vs. 68.2%, $p < 0.01$), improved resolution of shock (68.8% vs. 31.5%, $p < 0.01$), and reduced recurrence of shock within 72 h (8.7% vs. 20.7%, $p < 0.01$).

Conclusions: Addition of hydrocortisone to norepinephrine was associated with a lower 28-day mortality in patients with septic shock, compared to the addition of vasopressin.

KEYWORDS
hydrocortisone, norepinephrine, sepsis, septic shock, vasopressin

1 | INTRODUCTION

Septic shock is associated with circulatory, cellular, and metabolic dysfunction leading to mortality rates exceeding 40%.[1] The 2021 Surviving Sepsis Campaign (SSC) guidelines recommend the initiation of broad spectrum antibiotics, fluid resuscitation, and hemodynamic support.[2] Norepinephrine is the recommended first-line vasopressor to maintain a mean arterial pressure (MAP) greater than or equal to 65 mmHg; vasopressin or hydrocortisone may be considered for patients with ongoing vasopressor requirements.[2] Currently, evidence is lacking to guide selection of a second agent in patients receiving norepinephrine who require additional hemodynamic support.

Vasopressin has emerged as a treatment modality in septic shock based on the hypothesis that low vasopressin levels contribute to hypotension.[3] Exogenous vasopressin administration in patients with septic shock may restore vascular tone and blood pressure while decreasing catecholamine requirements.[4] This hypothesis has led to further studies investigating the efficacy of vasopressin in septic shock.[5,6] The Vasopressin and Septic Shock Trial (VASST) was the first landmark study to demonstrate a mortality benefit with the use of vasopressin, albeit only in a subgroup of patients with less severe shock.[5] Evidence remains limited regarding the benefits of vasopressin; however, initiation at a norepinephrine-equivalent dose of 0.25 to 0.5 mcg/kg/min has been suggested.[2]

The rationale for glucocorticoid administration relates to the hypothesis that exogenous steroids improve the relative adrenal insufficiency and hyperinflammatory state of patients with septic shock.[7] Furthermore, corticosteroids inhibit nitric oxide (NO) synthase which opposes sepsis induced NO-mediated vasodilation to restore hemodynamic stability.[8] Studies which have evaluated the use of hydrocortisone in patients with septic shock have demonstrated conflicting results on mortality while also demonstrating an improvement in clinical outcomes such as decreased time to shock reversal and shorter length of stay.[9–12] The SSC guidelines suggest that corticosteroids should be initiated at a norepinephrine-equivalent dose greater than or equal to 0.25 mcg/kg/min at least 4 h following vasopressor initiation.[2]

Significant practice variation exists when selecting between hydrocortisone and vasopressin as second line agents in patients with septic shock. This gap in evidence warrants further research to determine the most appropriate agent in patients with septic shock in need of escalating doses of norepinephrine. The purpose of this study is to compare clinical outcomes associated with the use of vasopressin versus hydrocortisone in patients with septic shock.

2 | METHODS

This multicenter, retrospective, observational, cohort study was conducted at ten hospitals across Ascension Health. A list of adult patients with an ICD-10 code for severe sepsis with septic shock (R65.21) receiving norepinephrine, and either intravenous hydrocortisone, vasopressin, or both, from December 2015 to August 2021 was evaluated in reverse chronological order to identify patients for inclusion. Subjects were included if the following criteria were met: (1) receipt of vasopressin (0.03 or 0.04 units/min) or IV hydrocortisone (200 or 300 mg/day), (2) receipt of norepinephrine prior to initiation of the study drug (vasopressin or hydrocortisone), (3) receipt of at least 30 mL/kg of IV fluid bolus prior to the addition of the study drug, (4) receipt of antibiotics for presumed septic shock, and (5) baseline lactate >2 mmol/L. Subjects were excluded if they were pregnant or incarcerated, received vasopressors or inotropes other than norepinephrine prior to study drug initiation, required mechanical circulatory support (e.g. VA-ECMO, Impella®), had a history of glucocorticoid use within the previous 6 months, received simultaneous initiation of norepinephrine and the study drug, or initiation of both vasopressin and hydrocortisone occurred within 6 h. Sepsis care was at the discretion of the treating clinician; no formal protocol existed to guide initiation or timing of either study drug. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.[13] Data collection was standardized by training all investigators on study definitions and use of our centralized data collection software, Research Electronic Data Capture (REDCap). A second investigator analyzed the compilation of data for outliers and missing data points. The Institutional Review Board at Ascension St. John Hospital approved the study as the coordinating site (Approval #1823455, 11/10/2021); respective institutional review board approvals were obtained through the Institutional Review Boards at Ascension Genesys Hospital (Approval #00004144, 11/10/2021), Ascension St. Vincent's Jacksonville (Approval # 1838980, 11/17/2021), and Ascension St. Vincent's Birmingham (Approval #00018001, 11/30/2021).

The primary outcome was mortality within 28 days of study drug initiation. Secondary outcomes included hemodynamic responsiveness, resolution of shock, recurrence of shock within 72 h, duration of vasopressor therapy, ICU length of stay, hospital length of stay, incidence of new renal replacement therapy (RRT), 28-day ventilator-free days, and incidence of adverse events.

Hemodynamic responsiveness, defined as attainment of a MAP of 65 mmHg or greater with a reduced vasopressor requirement compared to that at study drug initiation, was assessed at 3, 6, 12, and 24 h following study drug initiation. Resolution of shock was defined as the attainment of a MAP of 65 mmHg for more than 24 h without the use of vasopressors or inotropes. Recurrence of shock was defined as any new episode of hemodynamic instability requiring vasopressor therapy within 72 h following resolution of the initial episode of septic shock. Length of stay was calculated using the date of admission and discharge from the hospital and intensive care unit. Adverse effects evaluated include documentation of life-threatening arrhythmia, hyperglycemia (blood glucose >300 mg/dL), hyponatremia (serum sodium <130 mmol/L), hypernatremia (serum sodium >150 mmol/L), new bacteremia or fungemia (positive blood cultures with a different organism that was previously isolated during the initial shock, or presence of the same organism

after evidence of negative blood cultures), and clinically suspected gastrointestinal bleeding.

Baseline comorbidities were assessed at the time of hospital admission by chart review. Data collected at study drug initiation included norepinephrine dose, duration of norepinephrine prior to study drug initiation, receipt of mechanical ventilation, lactate level, and Sequential Organ Failure Assessment (SOFA) score. For calculation of SOFA score, multiple imputation was used to account for missing SOFA score component values.[14] Total vasopressor dosage was collected at 3, 6, 12, and 24 h to assess hemodynamic response and described in norepinephrine equivalents using the following formula: (norepinephrine [μg/kg/min]) + (epinephrine [μg/kg/min]) + (phenylephrine [μg/kg/min])/10 + (dopamine [μg/kg/min])/100 + (vasopressin [units/min])×2.5 + (angiotensin II [μg/kg/min])*10.[15]

2.1 | Statistical analysis

To determine the required sample size, a post-hoc sub study of the VASST trial by Russell et al. was reviewed.[16] This substudy found that the 28-day mortality rate in patients receiving steroids compared to those receiving vasopressin was 44.7% and 33.7%, respectively. To detect this 11% difference between groups with an alpha of 0.05, 307 subjects per group were required to achieve 80% power. To account for any loss of patients due to incomplete data, the sample size was increased by 20%, requiring 384 subjects in each group to be collected for analysis. Patient charts were reviewed in reverse chronological order until 384 eligible patients per treatment group were identified.

Categorical data was described using frequency distributions, while continuous data was described using mean with standard deviation or median with interquartile range, depending upon the distribution of the data. Univariable analysis for nominal data was performed using the chi-squared test and continuous variables were assessed using Student's *t*-test or the Mann–Whitney U test, depending upon the distribution of the data. Multivariable analysis utilized logistic regression. Variables were considered for inclusion in the multivariable model if they were theoretically associated with mortality and subsequently included if found to be associated with mortality on univariable analysis ($p < 0.1$). All data was analyzed using SPSS v. 28.0 and a *p*-value less than 0.05 was considered to indicate statistical significance.

A sensitivity analysis was performed utilizing greedy nearest neighbor propensity score matching. For the propensity analysis, matching was performed in a 1:1 ratio within 0.1 of the logit propensity score standard deviation. Variables were included in the model if they were theoretically associated with mortality and not expected to overlap with other variables. Patients were matched on age, SOFA score, baseline heart rate, lactate level, duration of norepinephrine prior to initiation of hydrocortisone or vasopressin, BMI, COVID-19 status, as well as a past medical history of diabetes, cancer, transplant, liver disease, hypertension, heart failure, and/or chronic kidney disease. Propensity score was assessed after matching by evaluating balancing of groups and distribution of propensity scores in quintiles, across the area of common support, and across the entire distribution.

3 | RESULTS

A total of 1698 subjects were screened for inclusion in this study with 768 subjects meeting inclusion criteria (Figure 1). The overall cohort median (interquartile range) SOFA score was 10 (8–13), norepinephrine dose was 0.3 mcg/kg/min (0.1–0.5 mcg/kg/min), and lactate was 3.8 mmol/L (2.4–7.0 mmol/L) at initiation of the study drug. Additional baseline characteristics are described in Table 1. Subjects in the vasopressin group were more severely ill than subjects in the hydrocortisone group in the unmatched cohort; significant differences were noted in lactate [5.0 mmol/L (2.8–8.6 mmol/L) vs. 3.1 mmol/L (2.2–5.1 mmol/L); $p < 0.01$], mechanical ventilation (72.9% vs. 56%, $p < 0.01$), baseline norepinephrine dose [0.4 mcg/kg/min (0.2–0.6 mcg/kg/min) vs. 0.2 mcg/kg/min (0.1–0.3 mcg/kg/min); $p < 0.01$], and MAP [64 mmHg (56–70 mmHg) vs. 69 mmHg (64–76 mmHg); $p < 0.01$]. Propensity score matching was successful for 290 matched pairs of patients who received vasopressin or hydrocortisone. Baseline characteristics following matching is summarized in Table 1.

The primary outcome, 28-day mortality, was significantly lower in the hydrocortisone group compared to the vasopressin group in the overall cohort (42.2% vs. 73.2%, OR 0.27; 95% CI 0.20–0.36). These results were consistent when analyzed according to geographic region

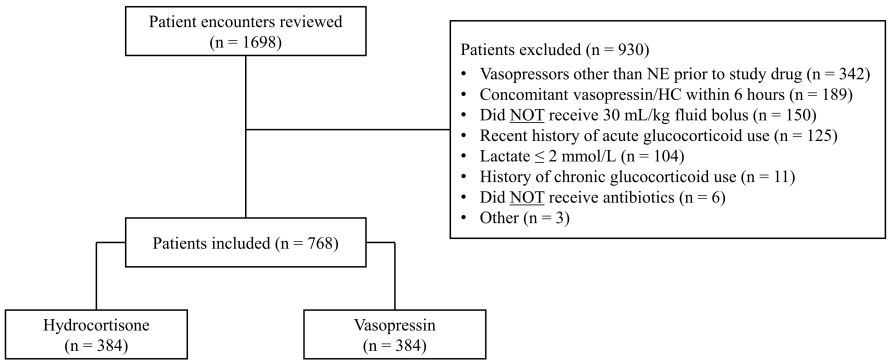

FIGURE 1 Flowchart of cohort inclusion and exclusion.

TABLE 1 Baseline characteristics in the overall and propensity score-matched cohort.

	Unmatched			Propensity score matched		
Variable	Vasopressin ($n=384$)	Hydrocortisone ($n=384$)	p-value	Vasopressin ($n=290$)	Hydrocortisone ($n=290$)	SMD
Age, years	69 (61–78)	69 (60–77)	0.81	70 (61–79)	70 (61–77)	0.05
Male	196 (51)	199 (51)	0.83	148 (51)	145 (50)	0.01
Caucasian	272 (70.8)	270 (70.3)	0.78	216 (74.5)	202 (69.7)	0.07
BMI (kg/m^2)	27.3 (22.7–32.9)	26.1 (22.3–31.2)	0.04	26.9 (22.3–32.7)	27.1 (22.5–31.7)	0.02
SOFA score	11 (9–13)	10 (8–12)	0.41	11 (9–12)	10 (9–13)	0.04
Lactate (mmol/L)	5.0 (2.8–8.6)	3.1 (2.2–5.1)	<0.01	3.9 (2.6–6.9)	3.5 (2.3–5.9)	0.09
Past medical history						
CKD	68 (17.7)	72 (18.8)	0.71	57 (19.7)	53 (18.3)	0.02
RRT	25 (6.5)	28 (7.3)	0.67	20 (6.9)	20 (6.9)	<0.01
DM	127 (33.1)	120 (31.3)	0.59	91 (31.4)	89 (30.7)	<0.01
HF	87 (22.7)	71 (18.5)	0.15	63 (21.7)	57 (19.7)	0.03
HTN	233 (60.7)	228 (59.4)	0.71	173 (59.7)	179 (61.7)	0.02
Liver disease	33 (8.6)	32 (8.3)	0.90	24 (8.3)	27 (9.3)	0.02
Cancer	82 (21.4)	60 (15.6)	0.04	51 (17.6)	50 (17.2)	<0.01
Mechanical ventilation	280 (72.9)	215 (56.0)	<0.01	199 (68.6)	166 (57.2)	0.12
COVID-19	21 (5.5)	11 (2.9)	0.07	14 (4.8)	11 (3.8)	0.03
Norepinephrine (NE) dose (mcg/kg/min)	0.4 (0.2–0.6)	0.2 (0.1–0.3)	<0.01	0.40 (0.23–0.60)	0.19 (0.10–0.35)	0.74
MAP (mmHg)	64 (56–70)	69 (64–76)	<0.01	64 (56–70)	68 (64–75)	0.54
Time from initiation of NE to study drug (hr.)	6.8 (3.3–14.4)	8.5 (4.1–17.6)	0.012	7.1 (3.3–16.8)	8.1 (4.2–16.3)	0.01

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; MAP, mean arterial pressure; RRT, renal replacement therapy; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment. All values are listed as median (IQR) or *n* (%).

of treatment center; severity of illness was noted to be similar across geographic regions. After controlling for potential confounders (BMI, cancer, liver disease, heart Failure, age, time between NE and study drug initiation, lactate at study drug initiation, baseline HR, SOFA, baseline NE dose, COVID-19), the results of a multivariable logistic regression were consistent with the univariate analysis, demonstrating a significantly lower 28-day mortality among patients receiving hydrocortisone (Table 2, OR 0.46 [95% CI, 0.32–0.66]). In the sensitivity analysis, the difference in 28-day mortality persisted in patients who received hydrocortisone versus vasopressin (46.9% vs. 66.9%, OR 0.44 [95% CI 0.31–0.61]). Although SOFA score was balanced between groups, assessment of propensity score matching revealed that differences between individual components of SOFA score remained. An additional logistic regression was performed to control for differences in mechanical ventilation, baseline MAP, and baseline norepinephrine dose, which produced a similar difference in 28-day mortality favoring hydrocortisone (OR 0.57 [95% CI 0.40–0.82]).

Receipt of hydrocortisone was also associated with a greater likelihood of achieving a hemodynamic response at any time point (91.9% vs. 68.2%, $p<0.01$). Details on the incidence of hemodynamic response at 3, 6, 12, and 24 h are provided in Figure 2. Furthermore,

TABLE 2 Multivariate logistic regression evaluating the association of hydrocortisone versus vasopressin and the association with 28-day mortality.

Variables	Odds ratio	95% CI	p-value
Hydrocortisone	0.46	0.21–0.66	<0.01
BMI	0.99	0.98–1.01	0.58
COVID-19	1.92	0.75–4.96	0.18
History of cancer	1.82	1.16–2.87	0.01
History of liver disease	1.69	0.90–3.18	0.10
History of heart failure	1.23	0.80–1.89	0.34
Age	1.04	1.02–1.05	<0.01
Time between NE and study drug initiation	0.99	0.99–1.00	0.77
Lactate at study drug initiation	1.11	1.06–1.16	<0.01
Baseline HR	1.01	1.00–1.02	0.02
SOFA	1.22	1.14–1.30	<0.01
Baseline NE dose	1.94	1.00–3.77	0.05

Abbreviations: NE, Norepinephrine; SOFA, Sequential Organ Failure Assessment.

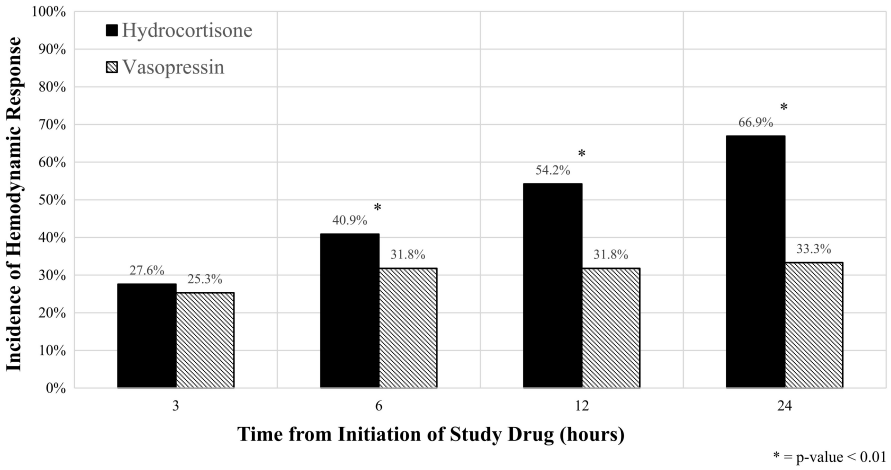

FIGURE 2 Association of hemodynamic response at 3, 6, 12, and 24 h for patients receiving hydrocortisone or vasopressin.

patients in the hydrocortisone group were more likely to achieve resolution of shock (68.8% vs. 31.5%, $p < 0.01$) with a lower recurrence of shock at 72 h following vasopressor discontinuation (8.7% vs. 20.7%, $p < 0.01$). When evaluating only those patients who survived, hydrocortisone was associated with a reduced hospital (12.5 vs. 19.5 days, $p < 0.01$) and ICU length of stay (5.5 vs. 9.5 days, $p < 0.01$) compared to vasopressin. Subjects in the hydrocortisone group had a greater number of 28-day mechanical ventilator-free days compared to subjects in the vasopressin group (14 vs. 0 days, $p < 0.01$). Further details of the secondary outcomes in both the unmatched and propensity score-matched cohort are listed in Table 3. Adverse effects were similar between groups, except for hypernatremia which occurred more frequently in the hydrocortisone group and cardiac arrest which occurred more frequently in the vasopressin group. Additional details on adverse effects are included in Table 4.

A post-hoc analysis was performed evaluating patients who required addition of the alternate study drug. Addition of hydrocortisone to vasopressin occurred in 12.7% of patients, whereas, vasopressin was added to hydrocortisone in 26.5% of patients ($p < 0.01$). For patients who received a single study drug, 28-day mortality was significantly lower in the hydrocortisone group compared to the vasopressin group (75.9% vs. 37.3%, $p < 0.01$). For patients who required addition of the alternate study drug, no difference in 28-day mortality was noted (65.7% vs. 75.5%, $p = 0.22$).

4 | DISCUSSION

Evidence is lacking to guide clinical decision making in the setting of hemodynamic instability despite norepinephrine use. Our study, the first to compare hydrocortisone and vasopressin in patients with septic shock, demonstrated a significant reduction in 28-day mortality with the use of hydrocortisone. Furthermore, patients who received hydrocortisone were more likely to achieve hemodynamic responsiveness and resolution of shock. Based on these results, hydrocortisone may be preferable to vasopressin for patients with septic shock and ongoing requirements for vasopressor therapy. However, these findings should be replicated in prospective clinical trials before widespread implementation.

Although a direct comparison between hydrocortisone and vasopressin is lacking, previous studies have investigated various combinations of these agents. The 2016 VANISH trial compared the effect of early vasopressin versus norepinephrine on kidney failure in patients with septic shock.[6] Patients were randomized to receive norepinephrine (up to 12 mcg/min) or vasopressin (up to 0.06 units/min).[6] Patients requiring support which exceeded these maximum doses were initiated on hydrocortisone or placebo.[6] If a patient remained hypotensive following hydrocortisone (or placebo), open label vasopressors were permitted.[6] The primary outcome, 28-day kidney failure free days, was similar between groups.[6] While this study was not powered to evaluate 28-day mortality, no significant differences were noted with vasopressin versus norepinephrine (30.9% vs. 27.5%) or hydrocortisone versus placebo (30.8% vs. 27.5%).[6] Extrapolation of these results to our research question is difficult as several aspects of the study are not consistent with standard of care, including the use of vasopressin as an initial vasopressor and titration up to 0.06 U/min. Additionally, of the 102 patients randomized to receive norepinephrine + hydrocortisone, only 68 ever received hydrocortisone, making evaluation of the treatment effect difficult.[6] In contrast to our study, no patients received the combination of norepinephrine and vasopressin.

The role of corticosteroids in septic shock has also been a subject of debate. The Annane et al. and Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial reported a significant reduction in all-cause mortality and improved shock reversal in patients with relative adrenal insufficiency who received corticosteroids.[12] Conversely, the Corticosteroid Therapy of Septic Shock (CORTICUS) trial and the Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL) trial failed to demonstrate an improvement in mortality, however, noted a shorter time to reversal of shock.[10,11] Differences in study outcomes may be related to inclusion criteria of the individual trials.[17] Studies which demonstrated a mortality benefit to corticosteroids included more severely ill patients, with a similar severity of

TABLE 3 Association of hydrocortisone versus vasopressin and outcomes in the overall and propensity score-matched cohort.

	Unmatched			Propensity score matched		
Outcome	Vasopressin ($n=384$)	Hydrocortisone ($n=384$)	p-value	Vasopressin ($n=290$)	Hydrocortisone ($n=290$)	p-value
28-day mortality	281 (73.2)	162 (42.2)	<0.01	194 (66.9)	136 (46.9)	<0.01
Hemodynamic response	262 (68.2)	353 (91.9)	<0.01	215 (74.1)	264 (91)	<0.01
Resolution of shock	121 (31.5)	264 (68.8)	<0.01	109 (37.6)	189 (65.2)	<0.01
Recurrence of shock within 72 h	25/121 (20.7)	23/264 (8.7)	<0.01	20/109 (18.3)	22/189 (11.6)	0.11
28-day ventilator-free days	0 (0–10)	14 (0–27)	<0.01	0 (0–19)	8 (0–25)	<0.01
New RRT initiation	63 (16.4)	42 (10.9)	0.08	45 (15.5)	38 (13.1)	0.41
ICU LOS[a] (days)	9.5 (5.5–17)	5.5 (3.5–10.5)	<0.01	8.5 (5.5–16.5)	5.5 (3.5–10.5)	<0.01
Hospital LOS[a] (days)	19.5 (12.5–30)	12.5 (8.5–21.5)	<0.01	18.5 (12.5–29.5)	13.5 (8.5–22.5)	<0.01

Abbreviations: LOS, length of stay.; RRT, renal replacement therapy. All values are listed as median (IQR), *n* (%) or *n*/*N* (%).

[a]Only survivors were included for LOS calculations.

TABLE 4 Association of hydrocortisone versus vasopressin and adverse events in the overall and propensity score-matched cohort.

	Unmatched			Propensity score matched		
Adverse event	Vasopressin ($n=384$)	Hydrocortisone ($n=384$)	p-value	Vasopressin ($n=290$)	Hydrocortisone ($n=290$)	p-value
Hyperglycemia	57 (14.8)	70 (18.2)	0.21	46 (15.9)	53 (18.3)	0.44
Hyponatremia	31 (8.1)	39 (10.2)	0.32	24 (8.3)	30 (10.3)	0.39
Hypernatremia	44 (11.5)	66 (17.2)	0.02	39 (13.4)	51 (17.6)	0.17
Gastrointestinal bleeding	18 (4.7)	17 (4.4)	0.86	10 (3.4)	14 (4.8)	0.40
New bacteremia / fungemia	10 (2.6)	17 (4.4)	0.17	8 (2.8)	12 (4.1)	0.36
Cardiac arrest	62 (16.1)	26 (6.8)	<0.01	36 (12.4)	24 (8.3)	0.10

Note: All values are listed as *n* (%).

illness as our study population based on SOFA score. Furthermore, CORTICUS and ADRENAL did not specify fluid resuscitation or vasopressor requirements for inclusion.[10,11] Our study had strict criteria for enrollment in both of these areas, based on the SEPSIS-3 definition. Time to corticosteroid initiation is another noted difference between these trials, with CORTICUS enrolling patients up to 72 h from the onset of shock, while our study enrolled patients on average 8 h from the onset of shock.

Although there is no formal recommendation from SSC with regard to the timing of corticosteroid initiation, this topic has been evaluated by several recent trials. A study by Ragoonanan et al. noted a shorter time to vasopressor discontinuation and reduced ICU length of stay in patients with early hydrocortisone initiation (≤12 h).[18] Similarly, a study by Sacha et al. noted that initiation of hydrocortisone within 12 h of shock onset was associated with a greater number of vasopressor-free days compared to initiation 48 h after shock onset.[19] This study also found lower rates of ICU mortality with early initiation of hydrocortisone.[19] In our study, the median time from norepinephrine to hydrocortisone initiation was 8.5 h, which may have positively influenced our results. Although our study was not powered to evaluate the impact of timing of initiation of hydrocortisone, our results coincide with emerging literature demonstrating improved outcomes with early hydrocortisone administration.

The timing of vasopressin initiation in patients with septic shock also remains controversial due to limited evidence. While the Vasopressin in Septic Shock (VASST) trial failed to demonstrate a difference in 28-day mortality, a subgroup analysis demonstrated a mortality benefit in patients with less severe shock (norepinephrine-equivalent dose of ≤15 mcg/min or lactate ≤1.4 mmol/L).[5] A 2022 study by Sacha et al. confirmed these findings, noting that high norepinephrine-equivalent dose and high lactate at vasopressin initiation were associated with increased in-hospital mortality.[20] The results of these studies suggest that earlier initiation of vasopressin, in patients with less severe septic shock, may be associated with improved outcomes. Patients in our study had a median norepinephrine-equivalent dose of 0.4 mcg/kg/min and lactate of 5 mmol/L at the time of vasopressin initiation, notably higher than VASST patients who had lower baseline norepinephrine requirements and an average serum lactate of 3.5 mmol/L. Furthermore, subjects in the VASST trial were excluded patients if death was anticipated within 12 h, which could explain lower mortality results

reported in this study. While rates of mortality in our vasopressin group were high, these results can be explained by a high severity of illness at the time of vasopressin initiation. This highlights the need for stronger evidence to define the optimal timing of initiation and agent for septic shock with escalation vasopressor requirements, as practice variation may be impacting mortality.

Strengths of our study include the multicenter, geographically diverse design encompassing subjects from ten hospitals across three different states to ensure external validity. To align with current guideline recommendations for the treatment of septic shock, we only included subjects who received a 30 mL/kg fluid bolus and antibiotics. Of note, appropriateness of antibiotics was not assessed; the use of antibiotics was only used to determine if a patient met study inclusion. Limitations of our study include the retrospective nature and reliance on accurate documentation of vasopressor doses. Our data collection process included data extraction across electronic medical records from different institutions performed by multiple parties. However, we accounted for potential errors by training all investigators on study definitions and performing extensive re-evaluation of raw data for omissions and outliers, which were re-assessed individually and corrected where appropriate. An additional limitation to the multicenter nature of this trial was a variety of prescribing practices among providers. No formal protocol was used to guide initiation of hydrocortisone or vasopressin at any of the participating sites, hence, it is difficult to explain why more critically ill patients were more likely to receive vasopressin. Significant practice variation exists in this population, which emphasizes the need for further research to define the optimal timing of initiation and agent for septic shock with escalating vasopressor requirements. Sepsis care was at the discretion of the treating clinician, hence, it is difficult to explain why patients with a higher severity of illness were more likely to receive vasopressin. Despite not having formalized protocols to guide initiation, the results we observed were consistent across sites; similar findings were observed following propensity score matching and multivariable logistic regression, strengthening our conclusions. Nevertheless, given the complexity of ICU patients, additional unidentified confounders may have contributed to our results. Given the retrospective nature of this study, the results are hypothesis generating and should be confirmed in future prospective trials.

5 | CONCLUSION

Addition of hydrocortisone to norepinephrine was associated with a lower 28-day mortality in patients with septic shock compared to addition of vasopressin. Additional benefits associated with the use of hydrocortisone included improved resolution of shock and hemodynamic responsiveness, reduced ICU and hospital length of stay, decreased shock recurrence, and a greater number of 28-day ventilator-free days. Patients initiated on vasopressin had a higher severity of illness, which highlights the need to reduce practice variation and prioritize future research defining the optimal approach to management of septic shock patients on escalating doses of norepinephrine.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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