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Original Research

CRITICAL CARE

Survival After Shock Requiring High-Dose Vasopressor Therapy

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Background: **Some patients with hypotensive shock do not respond to usual doses of vasopressor therapy. Very little is known about outcomes after high-dose vasopressor therapy (HDV). We sought to characterize survival among patients with shock requiring HDV. We also evaluated the possible utility of stress-dose corticosteroid therapy in these patients.**

Methods: **We conducted a retrospective study of patients with shock requiring HDV in the ICUs of five hospitals from 2005 through 2010. We defined HDV as receipt at any point of ≥ 1 μg/kg/min of norepinephrine equivalent (calculated by summing norepinephrine-equivalent infusion rates of all vasopressors). We report survival 90 days after hospital admission. We evaluated receipt of stress-dose corticosteroids, cause of shock, receipt of CPR, and withdrawal or withholding of life support therapy.**

Results: **We identified 443 patients meeting inclusion criteria. Seventy-six (17%) survived. Survival was similar (20%) among the 241 patients with septic shock. Among the 367 nonsurvivors, 254 (69%) experienced withholding/withdrawal of care, and 115 (31%) underwent CPR. Stress-dose corticosteroid therapy was associated with increased survival (*P* = .01).**

Conclusions: **One in six patients with shock survived to 90 days after HDV. The majority of nonsurvivors died after withdrawal or withholding of life support therapy. A minority of patients underwent CPR. Additionally, stress-dose corticosteroid therapy appears reasonable in patients with shock requiring HDV.** ***CHEST 2013; 143(3):664–671***

Abbreviations: ACS = abdominal compartment syndrome; APACHE = Acute Physiology and Chronic Health Evaluation; EMR = electronic medical record; HDV = high-dose vasopressor therapy; SOFA = Sequential Organ Failure Assessment

Shock is an often lethal syndrome of diminished or insufficient perfusion that impairs organ function. Generally associated with decreased arterial blood pressure, shock results most commonly from sepsis, hemorrhage, or primary cardiac failure.[1] Vasopressor medications, largely vasoactive catecholamine hormones, have been used for many decades in the treatment of hypotensive shock. These medications have not been subjected to rigorous, placebo-controlled studies, and consensus from clinical experience suggests that there is not equipoise for such a study in most cases of shock.[2] When vascular tone is profoundly diminished (eg, vasoplegic syndrome or distributive shock), patients may require high-dose vasopressor therapy (HDV).

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Vasopressor-refractory shock occurs when vasopressor therapy does not result in adequate arterial BP, despite sufficient extracellular fluid volume expansion. There is no consensus regarding the definition of vasopressor-refractory shock. Whether a requirement for particularly high vasopressor doses represents unrecoverable shock is not certain. Outcomes among patients receiving HDV are unclear because reports are generally limited to single-center studies that support contradictory conclusions.[3-6]

Using the highly detailed electronic medical record (EMR) of Intermountain Healthcare, we undertook a multicenter retrospective study to characterize survival among patients with shock that required HDV. We also sought to characterize the association between stress-dose glucocorticoid therapy and survival in this patient population. We previously presented preliminary results in abstract form.[7]

Materials and Methods

We studied all patients aged >16 years who were admitted from August 1, 2005, to August 31, 2010, to the ICUs of any of five hospitals and who received HDV, as defined later. These five hospitals represent a mixture of tertiary-care referral, community, and regional referral medical centers within Intermountain Healthcare, an integrated medical delivery system. Three study hospitals have academic training programs.

The Intermountain Healthcare EMR acquires data in real time from the infusion pumps used in ICUs. We initially identified all patients who received infusions ≥ 0.5 μg/kg/min of norepinephrine or epinephrine. Among those patients, we selected those whose norepinephrine equivalent (the sum of all vasopressors administered, expressed as equivalent doses of norepinephrine) was ≥ 1 μg/kg/min for ≥ 10 min. We estimated norepinephrine dose equivalences (e-Table 1) based on prior studies, emphasizing studies in septic adults[8-12] rather than children,[13,14] animal models,[15] or healthy adults.[16] Briefly, we considered 100 μg dopamine equivalent to 1 μg norepinephrine; 1 μg epinephrine equivalent to 1 μg norepinephrine; and 2.2 μg phenylephrine equivalent to 1 μg norepinephrine.

Because vasopressors are occasionally administered to normotensive patients (eg, to assure cerebral perfusion pressure in certain neurologic syndromes), we excluded patients who did not have hypotension as the reason for vasopressor therapy. We also excluded patients declared brain-dead and patients who received HDV exclusively during unsuccessful CPR.

We subdivided the causes of shock into sepsis, cardiac failure, immediately after cardiac arrest, hemorrhage/trauma, drug overdose, pulmonary embolism, pericardial tamponade, neurogenic, immediately post cardiac surgery, and other or uncertain, based on chart review. Where in-hospital cardiac arrest complicated another diagnosis (eg, sepsis), the patient was coded for the underlying diagnostic category rather than cardiac arrest. We calculated APACHE (Acute Physiology and Chronic Health Evaluation) II[17] and Sequential Organ Failure Assessment (SOFA)[18] scores for the day of admission, for the day on which the patient first received HDV, and for the day of peak vasopressor dose. We determined three maximum serum lactate levels: within 6 h of onset of HDV, within 6 h of onset of the peak dose of vasopressor therapy, and for the entire hospitalization. We also identified administration of stress-dose corticosteroids (at least 200 mg/24 h of IV hydrocortisone or equivalent), activated protein C, IV administration of ampoules of calcium gluconate/chloride, and IV administration of ampoules of sodium bicarbonate while the patient was receiving vasopressor therapy.

We determined mortality with the Intermountain Master Death Record, which incorporates results from Utah state vital statistics. Our primary outcome was 90-day all-cause mortality. We also determined digital or limb necrosis, incident ischemic or infarcted bowel, and abdominal compartment syndrome (ACS) from review of the EMR. We also recorded the incidence of decompressive laparotomy to treat ACS.

We determined whether patients had undergone in-hospital CPR or withdrawal or withholding of life support therapy (often termed "comfort care") by chart review. We did not consider full support with the exclusion only of chest compressions to represent withdrawal or withholding of care. We considered decisions to "not escalate care" to represent withholding of life support therapy. The Intermountain Healthcare institutional review board approved this study (#1020798), with waiver of informed consent.

Statistical Methods

We reported central tendencies as mean or median as dictated by normality of the data. We compared between or among group central tendencies with the Fisher exact test, Student *t* test, Wilcoxon rank-sum, or Kruskal-Wallis statistic as dictated by type of comparison and normality of the data. For logistic regression of mortality, we used a feature selection strategy that used repeated bootstrap sampling to maximize the area under the receiver operating characteristic curve in the "out of bag" sample (those observations not used to build the given model), a technique used to avoid over-fitting of the model.[19,20] Clinical features available at the initiation of HDV therapy and the norepinephrine-equivalent dose were retained if they improved the "out of bag" area under the receiver operating characteristic curve. We generated effect plots for the resulting model. To evaluate the association between stress-dose steroids and mortality, we used sensitivity analyses to control for immortal time bias in that association, including time-fixed Cox proportional hazards and time-dependent Cox proportional hazards. Immortal time bias exists when longer survival is incorrectly attributed to a treatment or other exposure.[21,22] This occurs in two related ways: (1) the death of a patient who does not survive long enough to receive the treatment is incorrectly attributed to lack of treatment, and (2) a patient's survival before a treatment has been given is incorrectly attributed to the treatment. The bias is called "immortal time" because patient follow-up time is included in the study, during which it is impossible for the patient to have died. We performed all analyses in the R Statistical Package, version 2.13 (The R Project for Statistical Computing).[23]

Results

Figure 1 summarizes the strategy that identified 443 patients who received HDV. Table 1 summarizes causes of shock, demographics, and illness-severity scores. Septic shock represented cause of shock in 54% (241 of 443) of patients. Table 2 summarizes survival within subgroups of shock, including distinct etiologies of septic shock. Patients receiving HDV for exsanguinating hemorrhage or after cardiac arrest had the lowest survival, and patients receiving HDV immediately after cardiac surgery had the highest survival.

Seventeen percent (76 of 443) of all patients receiving HDV and 20% (47 of 241) of septic patients

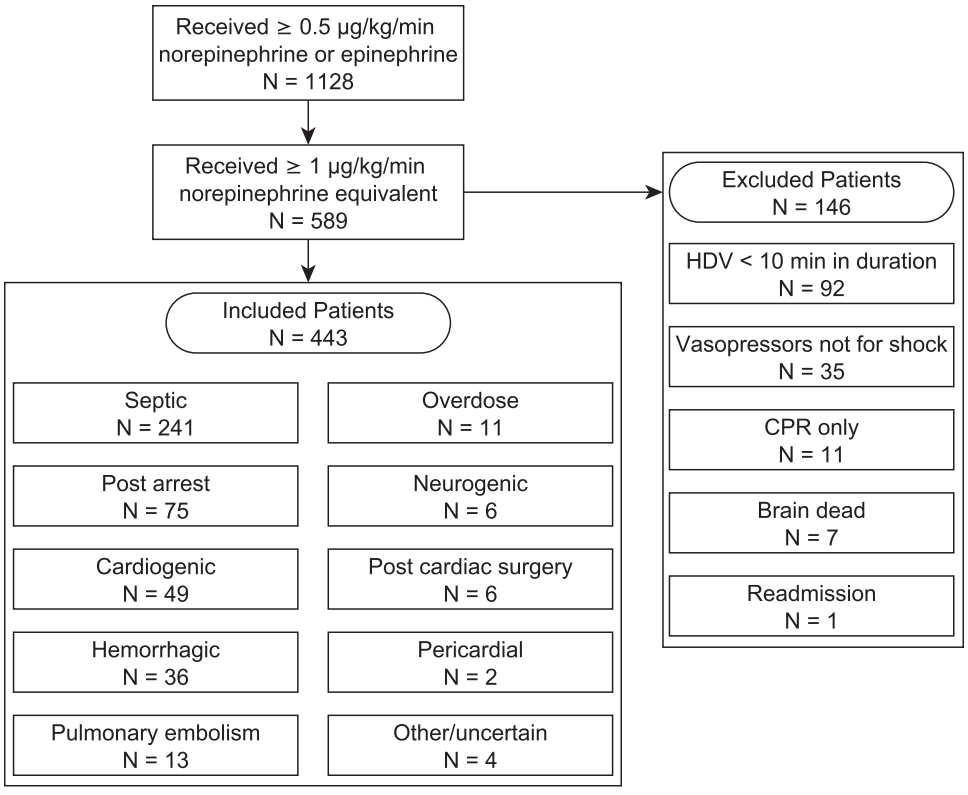

FIGURE 1. Flow chart representing patient selection process and diagnostic categories. HDV = high-dose vasopressor therapy.

receiving HDV survived. Survival decreased as maximal vasopressor dose increased (e-Fig 1). Most deaths occurred within 5 days after onset of HDV, as demonstrated in the Kaplan-Meier survival curves of e-Figure 2. Forty-one percent (76 of 184) of the patients who survived at least 24 h after onset of HDV survived.

Of the 89 patients with a maximum serum lactate concentration > 20 mM, 7% survived. The median of the maximum serum lactate concentration was significantly higher among nonsurvivors (13.2 mM) than among survivors (5.8 mM). Although statistically significant by the Kruskal-Wallis test ($P < .01$), peak lactate concentrations within 6 hours of onset of HDV (10.8 mM) or within 6 hours of onset of maximal vasopressor dose (11.7 mM) were not clinically different from overall maximum serum lactate concentration (12.1 mM).

On average, patients received, at most, three vasopressors simultaneously, with no statistically significant difference in number of vasopressors infused between survivors and nonsurvivors. The large majority (96%) of patients received norepinephrine; 55% of patients

Table 1—*Demographics and Severity Estimates by Cause of Shock*

Shock Cause	Patients, No.	Age, y	Maximal Vasopressor Dose (µg/kg/min)[a]	Maximal Lactate Concentration (mM)	APACHE II at Onset of HDV	SOFA at Onset of HDV
Sepsis	241	60	1.7	11.4	38	13
Cardiac arrest	75	60	1.6	14.0	38	14
Cardiogenic	49	63	1.5	12.7	31	13
Hemorrhage	36	62	1.9	12.5	38	14
Pulmonary embolism	13	66	2.1	8.1	39	11
Overdose	11	44	2.1	13.4	33	12
Neurogenic	6	26	1.8	5.8	31	10
Post cardiac surgery	6	58	1.2	8.0	22	12
Pericardial	2	48	1.4	13.1	32	14
Other	2	68	1.6	13.9	30	10
Uncertain	2	44	2.2	17.1	34	19

All data presented as median values. APACHE = Acute Physiology and Chronic Health Evaluation; HDV = high-dose vasopressor therapy; SOFA = Sequential Organ Function Assessment.

[a]Represents total simultaneous vasopressor dosage expressed in norepinephrine equivalents. See e-Table 1 for dose equivalencies used.

Table 2—*Survival, CPR, and Comfort Care by Cause of Shock*

Cause	90-d Survival, %	Underwent CPR After HDV, %[a]	Comfort Care Among Nonsurvivors, %
Sepsis	19.5	14.9	61.4
Pneumonia (n = 63)	10.4	18.5	77.6
Abdominal (n = 67)	23.8	19.7	75.6
Uncertain (n = 49)	22.4	8.5	91.4
Bacteremia (n = 28)	10.7	12.0	82.6
Urinary (n = 19)	36.8	5.9	41.7
Soft tissue (n = 12)	33.3	16.7	71.4
Other (n = 2)	0.0	0.0	0.0
Meningitis (n = 1)	0.0	0.0	0.0
Cardiac arrest[b]	6.7	65.3	68.5
Cardiogenic	20.4	34.7	46.9
Hemorrhage	5.6	34.4	60.6
Pulmonary embolism	7.7	45.5	72.7
Overdose	36.4	27.3	45.5
Neurogenic	16.7	0.0	50.0
Post cardiac surgery	66.7	0.0	33.3
Pericardial	50.0	0.0	50.0
Other	50.0	0.0	50.0
Uncertain	0.0	50.0	50.0

See Table 1 legend for expansion of abbreviation.

[a]Includes both survivors and nonsurvivors.

[b]Includes out-of-hospital and in-hospital cardiac arrest not attributable to another diagnostic category.

received epinephrine. Sixty-two percent of patients received fixed-dose vasopressin infusion, 33% of patients received phenylephrine, and 29% received dopamine.

Twenty-seven percent (120 of 443) of patients underwent in-hospital CPR; 4% (5 of 120) of patients who underwent in-hospital CPR survived to 90 days. Among nonsurvivors, withdrawal or withholding of life support therapies occurred in 69% (254 of 367) of patients. Eighteen percent of patients underwent dialysis; there was no statistically significant difference in receipt of dialysis between survivors and nonsurvivors. ACS (definite or suspected) occurred in 9% (42 of 443) of patients (23 definite, 19 suspected): 8% (6 of 76) in survivors and 10% (36 of 365) in nonsurvivors ($P = .8$). Of patients with ACS, 50% underwent decompressive laparotomy. All six survivors with definite or suspected ACS underwent decompressive laparotomy. If we restricted the analysis to patients in whom withdrawal of support did not prevent laparotomy, 62% of patients with definite or suspected ACS underwent decompressive laparotomy.

Table 3 outlines clinical differences between survivors and nonsurvivors. HDV was relatively brief: The median time at doses ≥ 1 μg/kg/min of norepinephrine equivalent was 122 min for survivors and 183 min for nonsurvivors. Incident digital or limb necrosis was documented in 8% of survivors and 1% of nonsurvivors; incident bowel ischemia or infarct was documented in no survivors and 5% of nonsurvivors.

Fifty percent of nonsurvivors and 61% of survivors received stress-dose corticosteroids ($P = .1$), a difference that persisted after controlling other predictors of mortality on logistic regression, as described later. Among patients with septic shock, 68% of survivors and 60% of nonsurvivors received stress-dose corticosteroids ($P = .3$.) In sensitivity analyses, we controlled for immortal time bias of the estimate of the

Table 3—*Differences in Characteristics Between Survivors and Nonsurvivors*

Characteristic	Survivors	Nonsurvivors	*P* Value
Maximum NE equivalent, μg/kg/min	1.4	1.8	< .01
Age, y	58	60	.08
Maximum lactate concentration, mM	5.8	13.2	< .01
Heart rate at onset of HDV, beats/min	110	112	.8
MAP at onset of HDV, mm Hg	65	65	.4
In-hospital CPR, %	6.6	33.1	< .01
Digital necrosis, %	7.9	1.4	.01
Incident bowel infarction, %	0	5.3	.06
Duration HDV, median, min	122	183	.05
ACS, %	7.9	9.8	.83
Decompressive laparotomy for ACS,[a] %	100	42	.02
Received stress-dose steroids, %	60.5	49.6	.11
Admission APACHE II score	35	37	.12
APACHE II score at onset of HDV	32	38	< .01
Admission SOFA score	11	12	.03
SOFA score at onset of HDV	12	13	< .01

All continuous values are median and all dichotomous data are proportions, unless otherwise indicated. ACS = abdominal compartment syndrome; MAP = mean arterial pressure; NE = norepinephrine. See Table 1 legend for expansion of other abbreviations.

[a]Proportion of patients with ACS who underwent decompressive laparotomy.

relationship between stress-dose steroids and mortality.[22] In a time-fixed Cox proportional hazards survival model, we measured survival from onset of HDV rather than hospital admission. On this analysis, steroids were associated with lower mortality (univariate $P = .03$, multivariate $P = .1$). In a time-dependent Cox proportional hazards survival model measuring survival from onset of HDV, the association between steroids and mortality was not significant (univariate $P = .5$, multivariate $P = .8$). In all models, the steroid effect was modified by vasopressin administration: On stratified regression, the apparent beneficial effect of steroids was larger among patients receiving vasopressin than among those not receiving vasopressin.

IV bolus bicarbonate was administered to 43% of all patients; IV calcium boluses were administered to 49% of patients. Activated protein C was administered to 15% of patients with septic shock (11% of survivors, 15% of nonsurvivors; $P = .5$). Tromethamine was rarely administered (2% of all patients).

The logistic regression model, after bootstrap feature selection, for 90-day mortality included maximal norepinephrine-equivalent dose, maximal serum lactate concentration, APACHE II score at the time of onset of HDV, and receipt of stress-dose corticosteroids (e-Table 2). Effect plots of predictors, depicting the relationship between a given predictor and mortality after controlling for all other predictors, are displayed in Figure 2. The relationship with lactate was sufficiently nonlinear to require using a natural spline with three knots. Mortality increased with higher norepinephrine-equivalent dose, lactate concentration, and APACHE II score, whereas mortality decreased with administration of stress-dose corticosteroids.

Discussion

This study, to our knowledge, reports on the largest cohort of patients yet published with shock severe enough to undergo HDV. Approximately one in six

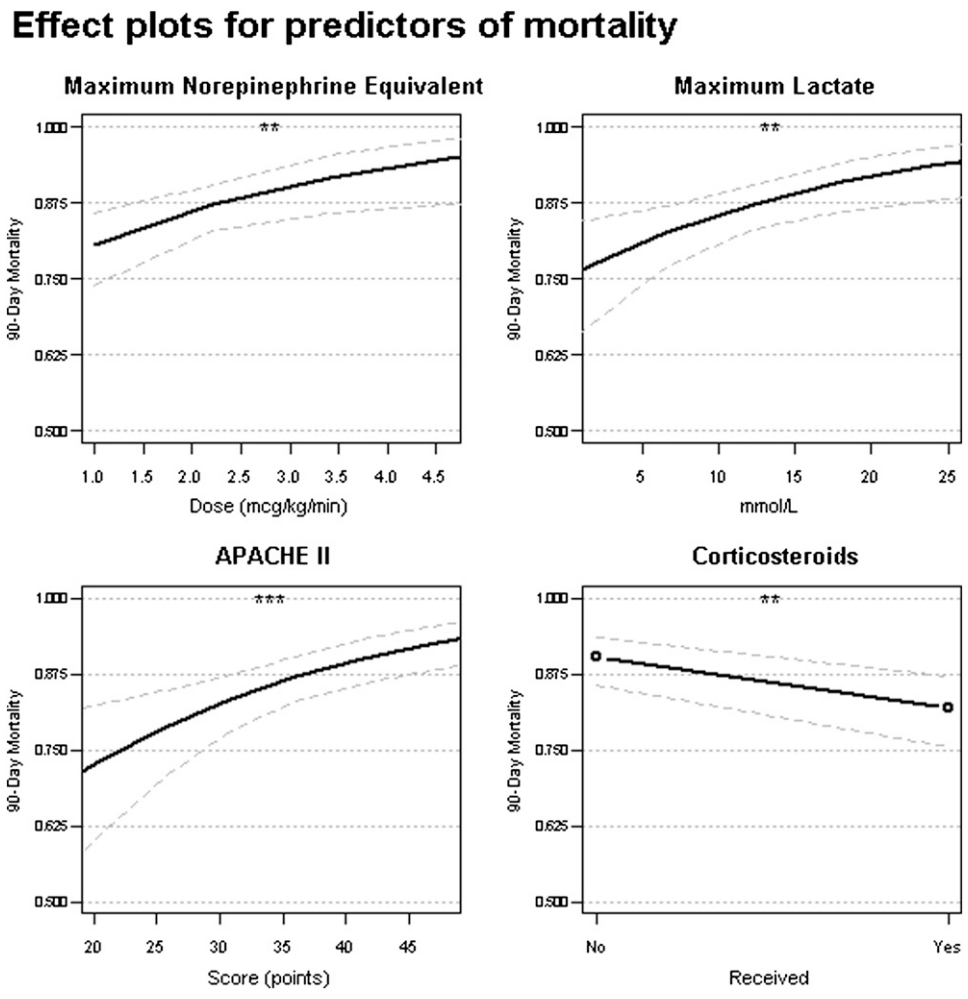

Figure 2. Effect plots for predictors included in final regression model. Plots depict relationship between predictor and mortality, with all other predictors held constant. Black line indicates effect estimate, dashed gray lines indicate 95% CIs for effect estimate. APACHE = Acute Physiology and Chronic Health Evaluation.

(17%) patients survived shock severe enough to undergo treatment with ≥ 1 μg/kg/min of norepinephrine equivalent. Withdrawal or withholding of care preceded death in two-thirds of nonsurvivors. While this study, lacking randomization of a therapy highly confounded by indication, does not assess whether HDV is harmful per se, it provides significant insight into outcomes from very severe shock of various etiologies. Although mortality tends to rise with increased HDV dose and very high doses (>2.5 μg/kg/min) of vasopressors were associated with only 5% survival, we do not believe that our data suggest a maximum dose of vasopressors. Instead, we believe that our data provide insight into prognosis in a group of extremely critically ill patients with severe shock. In addition, our study results are compatible with the utility of stress-dose glucocorticoid therapy in patients with shock severe enough to receive HDV, although this cannot be definitively concluded from a nonrandomized study.

Two, retrospective, cohort studies reported very low survival of patients receiving a vasopressor dose > 100 μg/min, including no survival among patients receiving > 200 μg/min of norepinephrine[3] and extremely high mortality among patients transitioned from 20 μg/kg/min of dopamine to continuous norepinephrine infusion.[5] In contrast, Martin et al[24] reported that five of 17 patients receiving similarly high-dose vasopressors survived. A study of a small, single-center, surgical ICU cohort in Greece suggested better outcomes, even with very high doses of norepinephrine.[4] Dunser et al[25] reported data from the placebo arm of an interventional trial in septic shock, which targeted mean arterial pressure ≥ 70 mm Hg among patients requiring a broad range of vasopressor support. Though the cohorts are not strictly comparable, the survival among 68 patients excluded from their cohort for failure to achieve a mean arterial pressure of 70 mm Hg (requiring a mean vasopressor load of 2.3 μg/kg/min) was 18%.[25]

Our study contributes to debates over the use of stress-dose corticosteroids in patients with severe shock.[26] Use of adjunct hydrocortisone in the treatment of shock generally diminished after publication of the pivotal Corticosteroid Therapy of Septic Shock (CORTICUS) trial.[27] However, mean vasopressor doses were lower in the CORTICUS trial than in antecedent trials,[28,29] and consensus recommendations continue to support use of stress-dose corticosteroids in refractory shock.[30] In this cohort, we noted that stress-dose corticosteroids were significantly associated with increased survival on time-fixed Cox proportional hazard models. The absence of statistical significance with time-dependent Cox proportional hazard modeling may reflect unopposed confounding by indication after controlling for immortal time bias. We were unable to control for confounding by indication and recognize that our analyses in this retrospective cohort cannot definitively decide the effect of stress-dose steroids in severe shock. The association between survival and glucocorticoid therapy in this cohort could serve to motivate a randomized controlled trial in patients receiving HDV for septic shock, although patient enrollment would be demanding (between 421 and 1,228 patients total for 80% power and $\alpha = 0.05$, depending on the distribution of covariates, effect size, and adequacy of randomization) based on the effect size observed in our study, the majority of patients die within the 24 h required for enrollment in many critical-care studies, and corticosteroids may need to be administered before onset of HDV to exert their full effect. In the absence of further evidence, which may be difficult to obtain, we believe that stress-dose corticosteroid therapy for patients receiving HDV remains reasonable. We found evidence for a statistical interaction between vasopressin therapy and corticosteroid therapy in this cohort. While the steroid benefit was most apparent among patients receiving vasopressin, our data do not address the utility of vasopressin either with or without steroids (such as was observed in the VASST [Vasopressin and Septic Shock Trial] study[31]).

Our study has several limitations. First, we did not collect quality-of-life outcomes. The lack of well-validated instruments for retrospective qualify-of-life assessments notwithstanding, we chose our mortality endpoint at 90 days to capture durable survival. Second, our study methodology does not allow us to determine the role that withdrawal/withholding of care plays in the high mortality associated with shock requiring HDV. Third, our methodology cannot exclude the possibility that the association between corticosteroid therapy and survival is biased and/or confounded. In addition, we cannot comment on whether HDV has a salutary or deleterious effect on survival in patients with severe shock. Whether permissive hypotension with lower doses of vasopressors would be beneficial in patients like ours is unknown.

Although our methodology was not designed to distinguish direct negative effects of HDV from the underlying shock that necessitated HDV, we were able to document side effects often attributed to HDV. Digital or limb ischemia, an oft-feared complication of HDV, was uncommon (7%) among survivors, although this may have been underreported in this cohort. Digital or limb ischemia was rare among nonsurvivors, although they may not have survived long enough for this complication to ensue. Although all survivors with ACS within this cohort underwent decompressive laparotomy, our methodology and sample size for this condition do not support reliable inferences about the indications for or efficacy of decompressive laparotomy.

Conclusions

One in six patients receiving HDV survived 90 days after hospital admission; withdrawal/withholding of care was common among nonsurvivors. Stress-dose corticosteroid therapy was associated with increased survival in patients receiving HDV for severe shock.

Acknowledgments

Author contributions: Dr Brown had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Brown: contributed to study conception; data acquisition, analysis, and interpretation; drafting the manuscript; revising the manuscript for important intellectual content; and approving the final copy and served as principal author.
Dr Lanspa: contributed to study conception, data acquisition, drafting the manuscript, revising the manuscript for important intellectual content, and approving the final copy.
Dr Jones: contributed to study conception, data analysis and interpretation, revising the manuscript for important intellectual content, and approving the final copy.
Dr Kuttler: contributed to data acquisition, revising the manuscript for important intellectual content, and approving the final copy.
Ms Li: contributed to data acquisition, analysis, and interpretation; revising the manuscript for important intellectual content; and approving the final copy.
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Additional information: The e-Figures and e-Tables can be found in the "Supplemental Materials" area of the online article.

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