

# Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock\*

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**Objective:** Vasopressin and corticosteroids are often added to support cardiovascular dysfunction in patients who have septic shock that is nonresponsive to fluid resuscitation and norepinephrine infusion. However, it is unknown whether vasopressin treatment interacts with corticosteroid treatment.

**Design:** Post hoc substudy of a multicenter randomized blinded controlled trial of vasopressin vs. norepinephrine in septic shock.

**Setting:** Twenty-seven Intensive Care Units in Canada, Australia, and the United States.

**Patients:** Seven hundred and seventy-nine patients who had septic shock and were ongoing hypotension requiring at least 5  $\mu\text{g}/\text{min}$  of norepinephrine infusion for 6 hours.

**Interventions:** Patients were randomized to blinded vasopressin (0.01–0.03 units/min) or norepinephrine (5–15  $\mu\text{g}/\text{min}$ ) infusion added to open-label vasopressors. Corticosteroids were given according to clinical judgment at any time in the 28-day postrandomization period.

**Measurements:** The primary end point was 28-day mortality. We tested for interaction between vasopressin treatment and corticosteroid treatment using logistic regression. Secondary end points were organ dysfunction, use of open-label vasopressors and vasopressin levels.

**Main Results:** There was a statistically significant interaction between vasopressin infusion and corticosteroid treatment ( $p = 0.008$ ). In patients who had septic shock and were also treated with corticosteroids, vasopressin, compared to norepinephrine, was associated with significantly decreased mortality (35.9% vs. 44.7%, respectively,  $p = 0.03$ ). In contrast, in patients who did not receive corticosteroids, vasopressin was associated with increased mortality compared with norepinephrine (33.7% vs. 21.3%, respectively,  $p = 0.06$ ). In patients who received vasopressin infusion, use of corticosteroids significantly increased plasma vasopressin levels by 33% at 6 hours ( $p = 0.006$ ) to 67% at 24 hours ( $p = 0.025$ ) compared with patients who did not receive corticosteroids.

**Conclusions:** There is a statistically significant interaction between vasopressin and corticosteroids. The combination of low-dose vasopressin and corticosteroids was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids. (Crit Care Med 2009; 37:811–818)

**KEY WORDS:** sepsis; septic shock; vasopressin; corticosteroids; randomized controlled trial

The mortality of septic shock varies from 30% to 60% (1–3). Ongoing hypotension despite fluid resuscitation is a major contributor to the high mortality. When

patients do not respond adequately to fluid and vasopressor resuscitation, vasopressin and/or corticosteroids are often added (3, 4).

Randomized controlled trials of vasopressin (5) and of corticosteroids (3) have recently been published. The Vasopressin and Septic Shock Trial (VASST) trial of vasopressin vs. norepinephrine in patients with septic shock found that vasopressin infusion did not significantly decrease 28-day mortality compared with norepinephrine (5). However, in patients who had less severe septic shock (norepinephrine infusion of 5–15  $\mu\text{g}/\text{min}$  at randomization), vasopressin decreased 28-day mortality compared with norepinephrine (26.5% vs. 35.7%,  $p = 0.05$ ). There are two large randomized placebo-controlled trials of corticosteroids in patients who have septic shock (3, 6). Annane et al (6) reported that corticosteroids, compared with placebo, decreased mortality in patients who had septic shock and who did not respond adequately to a corticotropin stimulation test.

Sprung et al (3) conducted Corticosteroid Therapy of Septic Shock (CORTICUS) in part because the results of Annane et al were not entirely significant before adjustments. Sprung et al (3) found no difference in mortality between corticosteroids and placebo.

Whether there is an interaction between vasopressin and corticosteroid treatment is unknown, yet many septic shock patients receive vasopressin and corticosteroids. The effects of corticosteroids on vasopressin are controversial. Corticosteroids increased vasopressin messenger RNA (7) and restored hemodynamic responsiveness to vasopressin infusion (8), had no effect on vasopressin levels (9), and even suppressed vasopressin gene expression (10, 11). Vasopressin (via V1b (V3) receptor) increases corticotroph responsiveness to corticotrophin releasing factor thereby increasing adrenocorticotrophic hormone (12) even when corticosteroid levels are increased (12–14). Therefore, vasopressin treatment

## \*See also p. 1126.

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**Table 1.** Baseline characteristics of patients who had septic shock according to corticosteroid treatment and vasopressin versus norepinephrine infusion

n	Steroids		p Value <sup>a</sup>	No Steroids		p Value <sup>b</sup>
	Norepinephrine 293	Arginine Vasopressin 296		Norepinephrine 89	Arginine Vasopressin 101	
Age (yrs.) (x ± sd)	61.4 ± 15.7	59.0 ± 16.2	0.06	63.1 ± 16.6	60.4 ± 17.2	0.28
Sex (n, % male)	176 (60.1)	183 (61.8)	0.66	53 (59.6)	63 (62.4)	0.69
Acute Physiology and Chronic Health Evaluation II (x ± sd)	27.9 ± 6.7	27.4 ± 7.2	0.41	24.7 ± 6.9	26.0 ± 8.9	0.28
Renal (n, %)	203 (69.5)	205 (69.3)	0.95	55 (62.5)	59 (58.4)	0.57
Respiratory (n, %)	264 (90.1)	261 (88.2)	0.45	77 (87.5)	81 (80.2)	0.18
Hematologic (n, %)	70 (24.0)	91 (30.7)	0.07	14 (15.9)	27 (26.7)	0.07
Neurologic (n, %)	67 (22.9)	78 (26.4)	0.33	22 (25)	23 (22.8)	0.72
Surgical (n, %)	94 (34.4)	105 (37.1)	0.51	38 (47.5)	46 (49.5)	0.78
Less severe shock (n, %)	126 (43.0)	131 (44.3)	0.76	56 (62.9)	65 (64.4)	0.84
More severe shock (n, %)	167 (57.0)	165 (55.7)		33 (37.1)	36 (35.6)	
Activated protein C (n, %)	53 (18.1)	52 (17.6)	0.87	3 (3.4)	9 (8.9)	0.12

<sup>a</sup>Statistical test ( $\chi^2$  or *t* test) comparing steroids plus norepinephrine vs. steroids plus vasopressin (Arginine vasopressin); <sup>b</sup>Statistical test ( $\chi^2$  or *t* test) comparing no steroids plus norepinephrine vs. no steroids plus vasopressin (Arginine vasopressin).

may interact with corticosteroid treatment in septic shock.

Accordingly, our hypothesis was that there is a significant interaction of vasopressin and corticosteroid treatment in septic shock. We had the unique opportunity to test this hypothesis in a *post hoc* analysis of the VASST trial (5) because many patients in that trial received corticosteroids in their clinical care.

## METHODS

VASST (5) is a multicenter blinded randomized controlled trial of vasopressin vs. norepinephrine in patients with septic shock. VASST was approved by the research ethics boards of all participating institutions. Patients, next of kin or surrogate decision maker, gave written informed consent.

**Selection Criteria.** Patients ( $\geq 16$  years of age) with septic shock unresponsive to fluids and at least 5  $\mu\text{g}/\text{min}$  norepinephrine infusion [or equivalent as defined (5)] were evaluated for enrollment. Septic shock was defined by two or more systemic inflammatory response syndrome criteria, (15) proven or suspected infection, hypotension despite fluid resuscitation, vasopressor infusion (at least 5  $\mu\text{g}/\text{min}$  of norepinephrine or equivalent) for 6 hours, and at least one new organ dysfunction. Exclusion criteria, blinding and randomization have been reported previously (5).

**Study Drug Infusion.** Study drug infusion began at 5 mL/hr and increased to 15 mL/hr (vasopressin, 0.01–0.03 U/min; norepinephrine, 5–15  $\mu\text{g}/\text{min}$ ) whereas open-label vasopressors were titrated to mean arterial pressure of 65–75 mm Hg. If the target mean arterial pressure could not be reached on maximal study drug, open-label vasopressors were increased. Study drug continued until the patient died, had a serious adverse

**Table 2.** Hydrocortisone dose (mg/day) and number of patients (n) treated with hydrocortisone each day in norepinephrine and vasopressin treatment groups

Study Day Number	Hydrocortisone Dose (mg/day), X ( $\pm$ sd), NE Group	n (NE)	Hydrocortisone Dose (mg/day), X ( $\pm$ sd), AVP Group	n (AVP)
1	160.1 (105.4)	173	154.7 (92.4)	194
2	218 (90.6)	208	216.9 (81)	221
3	226.7 (102.6)	198	226.8 (216.2)	202
4	218.2 (86.6)	174	199.7 (112.2)	182
5	206.2 (91.9)	167	184 (84.8)	159
6	196.4 (94.4)	147	182.2 (82.1)	135
7	188.5 (92)	125	168.2 (81.7)	117
8	169.7 (92.1)	108	164.7 (86.2)	91
9	165.1 (97.6)	85	147 (83.3)	76
10	174.6 (99)	67	142.2 (86)	64
11	185.2 (107.9)	55	137.4 (91)	56
12	170.2 (105.2)	52	121.2 (82)	49
13	169.4 (106.1)	45	134.7 (100.7)	43
14	159.8 (100)	39	139.6 (95.3)	37
15	185.3 (114.3)	35	161.4 (107.3)	28
16	185.8 (113.7)	31	160.2 (107.9)	27
17	185.8 (110.5)	30	153.4 (98.3)	31
18	175.5 (97)	31	157.7 (100.2)	26
19	178.4 (99.7)	32	142.5 (93.3)	26
20	189.5 (96.6)	29	136.7 (90.4)	24
21	164 (96.5)	31	140.9 (99.9)	22
22	149.8 (84.6)	27	121.3 (96.4)	20
23	151 (91.7)	23	172.3 (117.3)	15
24	144.3 (100.3)	22	175.4 (74.4)	14
25	153.8 (101.1)	20	166.1 (67.7)	14
26	169 (110.6)	21	152.9 (82.6)	14
27	166.7 (100.4)	18	156.9 (82)	13
28	181.7 (93.8)	15	132.1 (64.6)	14

NE, norepinephrine; AVP, vasopressin.

event, or improved (open-label vasopressors not required). Study drug was weaned when the target mean arterial pressure had been achieved for 8 hours with no open-label vasopressors. Open-label vasopressin and crossover to the opposite arm were prohibited.

**Use of Corticosteroids.** The administration of corticosteroids was not protocolized in this

trial but was determined by clinicians caring for the patients at each center. The type, dose, and route of administration of all corticosteroids were recorded in all patients over the 28-day primary observation period. We defined “use of corticosteroids” for this study as the administration of corticosteroids for at least 1 day during the 28-day observation period. Patients were accordingly classified as cortico-

steroid treatment or no-corticosteroid treatment.

**Plasma Vasopressin Levels.** Plasma was collected for measurement of vasopressin levels in a convenience sample of patients at six of the participating institutions (n = 107) as previously described (5).

**Statistical Analysis.** The primary outcome measurement was 28-day mortality. Vasopressin treatment-by-steroid interaction was assessed using logistic regression analysis (interaction statistics):  $P(\text{Death}) \sim \text{vasopressin} + \text{steroids} + \text{vasopressin} \times \text{steroids}$ .

Survival was also presented as Kaplan-Meier survival curves and all four survival curves (vasopressin or norepinephrine and corticosteroids or not) were compared with the log-rank test statistic.

Secondary outcomes were 1) 90-day mortality, 2) days alive and free from organ dysfunction over the first 28 days, according to the Brussels criteria (16). Secondary outcomes were compared using parametric procedures (independent Student's *t* test), non-parametric procedures (Mann-Whitney *U* test), or the Fisher's exact test, as appropriate. Analysis was conducted using Statistical Analysis Software software (version 9.1.3) (SAS Institute, Cary, NC) and Statistical Package for Social Scientists (version 15.0.1) (SPSS Inc., Chicago, IL).

## RESULTS

In VASST, 589 patients were treated with corticosteroids, 296 with both vasopressin and corticosteroids and 293 with both norepinephrine and corticosteroids (of 779 total patients). Within this subgroup of patients who received corticosteroids, vasopressin and norepinephrine patients were well matched except that the vasopressin-treated patients were somewhat younger (Table 1). A total of 190 patients were not treated with corticosteroids; 101 treated with vasopressin and 89 treated with norepinephrine. Within this subgroup vasopressin and norepinephrine patients were well matched (Table 1). Assignment to corticosteroid treatment was not randomized or blinded but was at the discretion of the treating physician, so the corticosteroid treatment subgroup had increased severity of illness compared with the no-corticosteroid treatment subgroup by many baseline measures (Table 1). Therefore, in the survival analysis we did not compare corticosteroid treatment to no-corticosteroid treatment but, rather, compared vasopressin to norepinephrine within each corticosteroid subgroup and tested for interaction.

There were no differences in the hydrocortisone dose (mg/day) and numbers of patients treated each day between the norepinephrine and vasopressin groups (Table 2). There were some patients on methylprednisolone (e.g., day 1 norepinephrine group n = 17, vasopressin group n = 17), some on dexamethasone (norepinephrine

group n = 11, vasopressin group n = 9), some on fludrocortisone (norepinephrine group n = 7, vasopressin group n = 15), and some on prednisone (norepinephrine group n = 6, vasopressin group n = 8). However, there were no differences between the use of these corticosteroids between the norepinephrine and vasopressin groups.

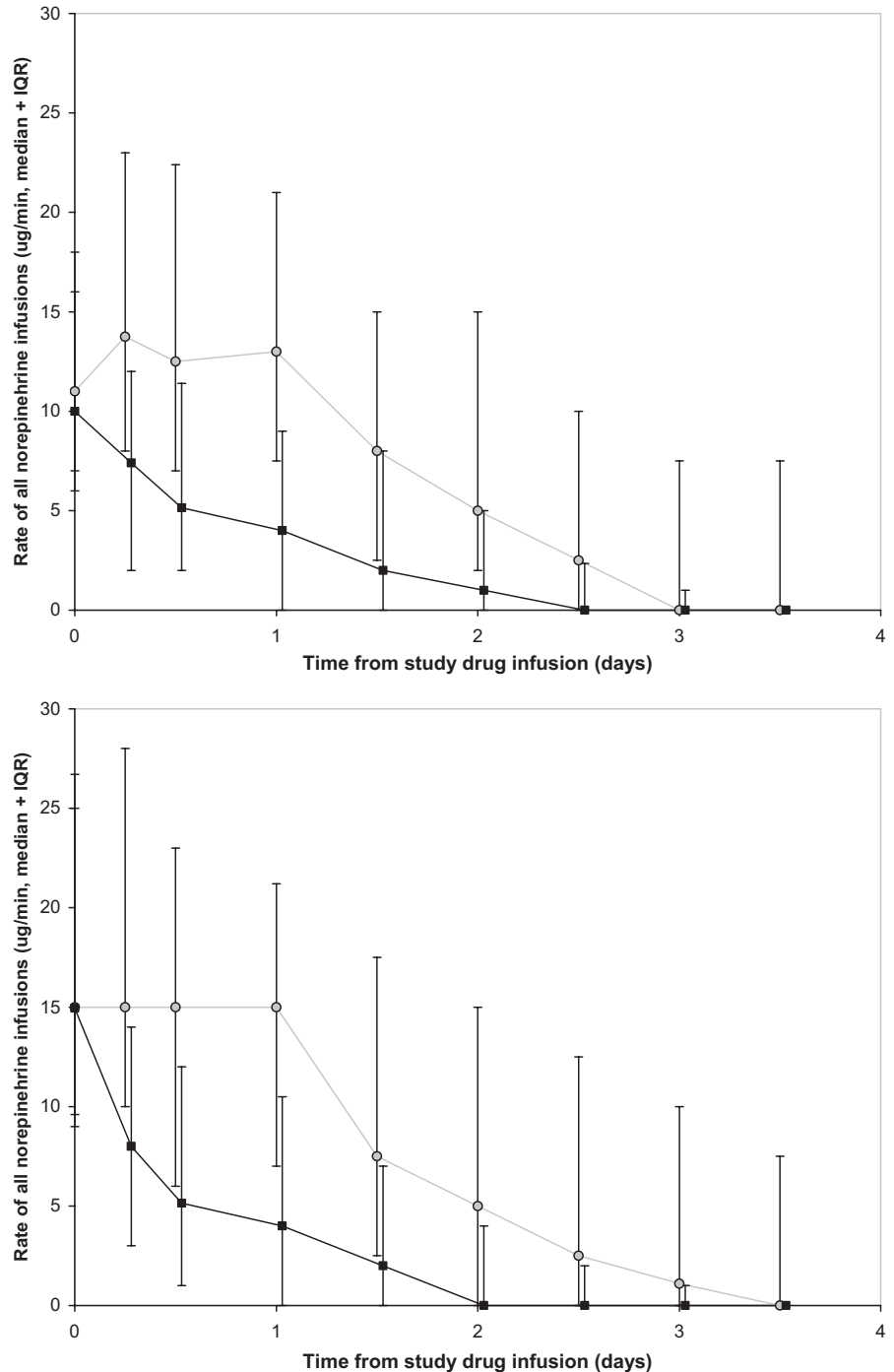


Figure 1. Rates of total norepinephrine infusion (open-label and study drug) in patients not receiving steroids in the top and in patients receiving steroids in the bottom. The vasopressin treated group is shown in black squares and the norepinephrine-treated group in gray circles. Values are median + interquartile range (IQR).

**Table 3.** Analysis of the rates of death from any cause for patients who had septic shock according to corticosteroid treatment and vasopressin versus norepinephrine infusion

n	Steroids		p Value <sup>a</sup>	No Steroids		p Value <sup>b</sup>
	NE 293	AVP 295		NE 89	AVP 101	
28-day mortality (%)	131 (44.7)	106 (35.9)	0.03	19 (21.3)	34 (33.7)	0.06 0.008 <sup>c</sup> 0.007 <sup>d</sup>
Days alive and free of organ dysfunction <sup>e</sup>			<sup>e</sup>			<sup>f</sup>
Cardiovascular	12 (0, 23)	18.5 (0, 24)	0.09	22 (12, 25)	19 (0, 24)	0.07
Vasopressor use	12 (0, 24)	19 (0, 24)	0.11	22 (12.25, 25)	20 (0, 24)	0.08
Respiratory	2 (0, 14)	4 (0, 16)	0.13	2 (0, 14)	2 (0, 16)	0.77
Ventilation	3 (0, 18.75)	8 (0, 20)	0.03	15.5 (0, 24)	12 (0, 21)	0.16
Renal	15 (2, 28)	21 (4, 28)	0.07	28 (7, 28)	22 (2, 28)	0.06
Renal replacement therapy	18 (4, 28)	24 (5, 28)	0.15	28 (16.5, 28)	28 (6, 28)	0.06
Hepatic	20 (2, 28)	24.5 (5, 28)	0.18	28 (11.25, 28)	25 (4.5, 28)	0.06
Hematologic	21 (2, 28)	23 (3, 28)	0.16	28 (19, 28)	28 (6, 28)	0.16
Neurologic	10.5 (0, 23)	15 (0.75, 24)	0.43	22 (10.5, 27)	15 (0, 24)	0.01
Days alive and free of any organ failure	0 (0, 3)	0 (0, 9)	0.02	0 (0, 10.75)	0 (0, 9)	0.27

NE, norepinephrine; AVP, vasopressin.

<sup>a</sup>Statistical test ( $\chi^2$ ) comparing steroids plus NE vs. steroids plus AVP; <sup>b</sup>statistical test ( $\chi^2$ ) comparing no steroids plus NE vs. no steroids plus AVP; <sup>c</sup>interaction statistic by logistic regression; <sup>d</sup>age-adjusted interaction statistic by logistic regression; <sup>e</sup>statistical test (Mann Whitney *U* test) comparing steroids plus NE vs. steroids plus vasopressin AVP; <sup>f</sup>statistical test (Mann Whitney *U* test) comparing no steroids plus NE vs. no steroids plus AVP; <sup>g</sup>DAF, days alive and free calculations. Organ dysfunction for each organ system was defined as being present during each 24-hr period if there was evidence of moderate, severe, or extreme organ dysfunction (Brussels criteria) (16). Increasingly severe organ dysfunction is shown by a low score (i.e. low score shows fewer days alive and free of organ dysfunction). Values are median (interquartile range); *p* values are based on Mann Whitney *U* test.

Vasopressin decreased total norepinephrine dose similarly in corticosteroid- and noncorticosteroid-treated patients (Fig. 1).

For the entire VASST cohort, vasopressin was not associated with a reduction in 28-day mortality (35.4%) compared with norepinephrine (39.3%,  $p = 0.26$ ) (5) and organ dysfunction rates did not differ between treatment groups (5).

In patients who received at least 1 day of corticosteroid treatment, vasopressin was associated with lower 28-day mortality (35.9% and 44.7%, respectively,  $p = 0.03$ ) and 90-day mortality (45.2% and 55.5% respectively,  $p = 0.01$ ) compared with norepinephrine (Table 3, Fig. 2). In contrast, if patients were not treated with corticosteroids, vasopressin was associated with a trend to increased mortality compared with norepinephrine (33.7% vs. 21.3%, respectively,  $p = 0.06$ ). The interaction between vasopressin treatment and corticosteroid treatment was highly statistically significant ( $p = 0.008$ ). The logistic regression interaction statistic remained significant after adjustment for age ( $p = 0.007$ ) and after adjustment for age, gender, Acute Physiology and Chronic Health Evaluation II and severity of shock stratum ( $p < 0.02$ ).

In patients who received corticosteroid treatment, the vasopressin group may have had less organ dysfunction as

suggested by trends to increased days alive and free from shock ( $p = 0.09$ ), ventilation ( $p = 0.03$ ), renal failure ( $p = 0.07$ ), and any organ failure ( $p = 0.02$ ) (Table 3). In contrast, in patients who were not treated with corticosteroids, the pattern of organ dysfunction in the vasopressin group was directionally opposite for all these organ failures. We note that differences in days alive and free from organ dysfunction are influenced by differences in mortality, and so assessment of organ dysfunction is difficult. Therefore, we determined days free from organ dysfunction in survivors only (Table 4). In patients who received corticosteroid treatment, there was a trend ( $p = 0.08$ ) to more days free from any organ dysfunction in the vasopressin group.

Low-dose vasopressin infusion significantly increased vasopressin levels (Fig. 3). In patients who were treated with vasopressin, corticosteroid treatment significantly increased vasopressin levels by 33% (6 hours) and by 67% (24 hours;  $p = 0.006$  and  $p = 0.025$ , respectively) compared with patients who did not receive corticosteroids (Fig. 3). Plasma vasopressin levels were extremely low, did not change over time, and were not altered by corticosteroids in the norepinephrine group (Fig. 3).

Overall rates of serious adverse events were similar in the two treatment groups

in both the corticosteroid treatment and no-corticosteroid treatment patients (Table 5). There was a significantly higher rate of cardiac arrests in norepinephrine patients treated with corticosteroids (2.4% vs. 0.3%,  $p = 0.04$ ).

## DISCUSSION

The primary finding of this retrospective analysis is that low-dose vasopressin infusion plus corticosteroids was associated with lower 28-day mortality compared with norepinephrine plus corticosteroids (35.9% vs. 44.7%,  $p = 0.03$ ) in septic shock. The combination of low-dose vasopressin infusion plus corticosteroids, compared with norepinephrine plus corticosteroids, was also associated with less organ dysfunction as shown by more days alive and free from shock, ventilation, and renal failure. In contrast, if patients were not treated with corticosteroids, vasopressin was associated with a trend to increased mortality compared with norepinephrine (33.7% vs. 21.3% respectively,  $p = 0.06$ ). This result is hypothesis generating.

The difference in response to vasopressin according to corticosteroid treatment was highly significant (interaction statistic  $p = 0.008$ ). Also, in patients who received vasopressin infusion, corticosteroid treatment (compared with

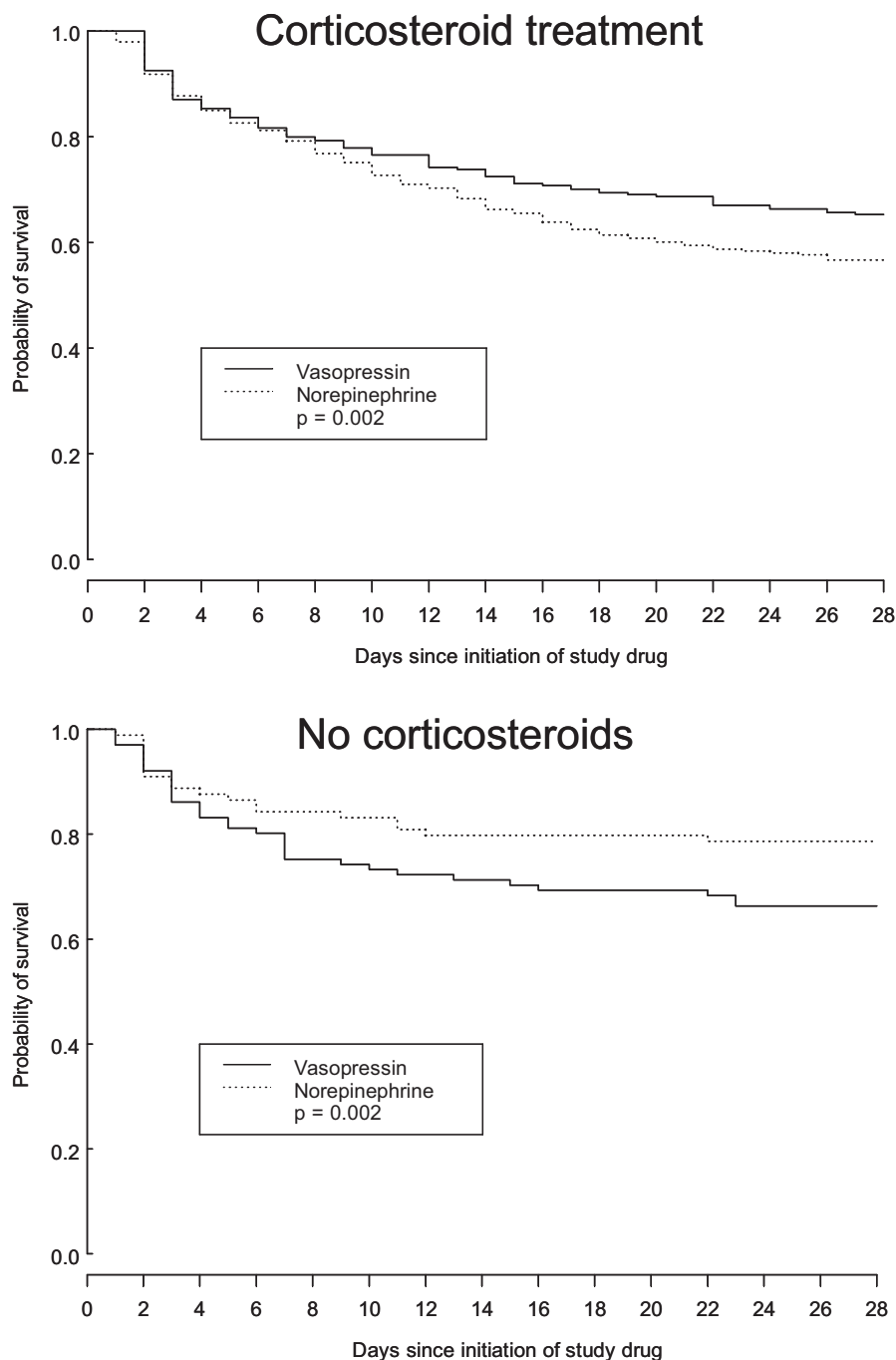


Figure 2. Kaplan-Meier survival curves for 28 days are shown for all patients according to vasopressin (solid lines) vs. norepinephrine (dashed lines) group and according to whether patients did (*top*) or did not (*bottom*) receive corticosteroids. For patients receiving corticosteroid treatment, survival was greater for vasopressin-treated patients. In contrast, for patients receiving no corticosteroids, survival was less for vasopressin-treated patients. These survival curves differ ( $p = 0.002$  by log-rank test).

no-corticosteroid treatment) increased vasopressin levels by 33% (6 hours) and by 67% (24 hours;  $p = 0.006$  and  $0.025$ , respectively). Corticosteroids did not increase vasopressin levels in the norepinephrine group. We believe that changes in vasopressin levels in response to corticosteroids may be re-

lated to the baseline level of vasopressin; thus, corticosteroids did not increase in vasopressin levels in the norepinephrine group because vasopressin levels were very low.

To our knowledge, this is the first clinical study of the interaction of vasopressin and corticosteroids on mortality and

organ dysfunction in human septic shock.

The effect of corticosteroids on mortality of septic shock is controversial (17). Hydrocortisone and fludrocortisone decreased mortality of patients who had septic shock and an impaired response to corticotropin (6). Sprung et al (3) found that hydrocortisone, compared with placebo, did not change mortality of patients who had septic shock and an impaired response to corticotropin (CORTICUS). There were differences between Annane and CORTICUS including mortality (e.g., Annane nonresponders: hydrocortisone 53%, placebo 63%; CORTICUS nonresponders: hydrocortisone 39%, placebo 36%). Our results add new information to the history of uncertainty surrounding the effects of corticosteroid treatment during sepsis. Corticosteroids clearly interact with many signaling pathways relevant during human sepsis.

Low-dose vasopressin decreases the dose of infused norepinephrine (18, 19), increases urine output, and improves renal function (19, 20). VASST found no difference in mortality of septic shock (5). However, low-dose vasopressin infusion was associated with a significant decrease in mortality compared with norepinephrine in less severe septic shock.

Both vasopressin (18–20) and corticosteroids (3, 6) increase responsiveness to endogenous and infused catecholamine vasopressors. Vasopressin decreased dose of norepinephrine compared with norepinephrine in both corticosteroid- and non-corticosteroid-treated patients.

We did not address the mechanism of the potential benefit of the combination of low-dose vasopressin plus corticosteroids compared with norepinephrine plus corticosteroids. One potential mechanism could be increased vasopressin levels induced by corticosteroids (Fig. 3). Other mechanisms include enhanced responsiveness to vasopressin conferred by corticosteroids (8) and more anti-inflammatory effects of the combination of vasopressin and corticosteroids.

Substantial evidence exists for a mechanistic connection between corticosteroid and vasopressin signaling pathways. There are complex interactions of the hypothalamic-pituitary-adrenal axis with the hypothalamic-posterior pituitary-vasopressin axis. The effects of corticosteroids on vasopressin are controversial: corticosteroids increase (7), do not change (9) and even decrease vasopressin

Table 4. Days free of organ dysfunction (brussels score) in survivors according to corticosteroid treatment and vasopressin vs. norepinephrine infusion

Days Free of Organ Dysfunction <sup>a</sup>	Steroids			Steroids		
	NE	AVP	p Value <sup>b</sup>	NE	AVP	p Value <sup>c</sup>
Cardiovascular	22 (17, 25)	23 (19, 25)	0.54	23 (21, 25)	23 (19, 25)	0.71
Vasopressor Use	23 (17, 25)	23 (19, 25)	0.62	23 (21, 25)	23 (20, 25)	0.75
Respiratory	9 (1, 19)	12 (3, 20)	0.19	6 (1, 17)	11.5 (1, 20)	0.25
Ventilation	17 (5, 22)	18 (8, 23)	0.24	19 (12, 24)	19 (9, 24)	0.59
Renal	26.5 (17, 28)	27 (20, 28)	0.56	28 (25, 28)	28 (21, 28)	0.48
Renal replacement	28 (22, 28)	28 (23, 28)	0.92	28 (28, 28)	28 (28, 28)	0.67
Hepatic	28 (25, 28)	28 (23, 28)	0.5	28 (25, 28)	28 (25, 28)	0.48
Hematologic	28 (23, 28)	28 (23, 28)	0.93	28 (28, 28)	28 (26, 28)	0.76
Neurologic	22 (15, 27)	22 (15, 26)	0.41	24 (18.5, 27.5)	21 (13.5, 26)	0.07
Any organ dysfunction	1 (0, 13)	4 (0, 15)	0.08	2 (0, 14)	2 (0, 15)	0.9

NE, norepinephrine; AVP, vasopressin.

<sup>a</sup>DAF, Days free calculations in survivors only. Organ dysfunction for each organ system was defined as being present during each 24-hr period if there was evidence of moderate, severe, or extreme organ dysfunction (Brussels criteria)<sup>16</sup>; <sup>b</sup>statistical test (Mann Whitney U test) comparing steroids plus NE vs. steroids plus AVP; <sup>c</sup>statistical test (Mann Whitney U test) comparing no steroids plus NE vs. no steroids plus AVP.

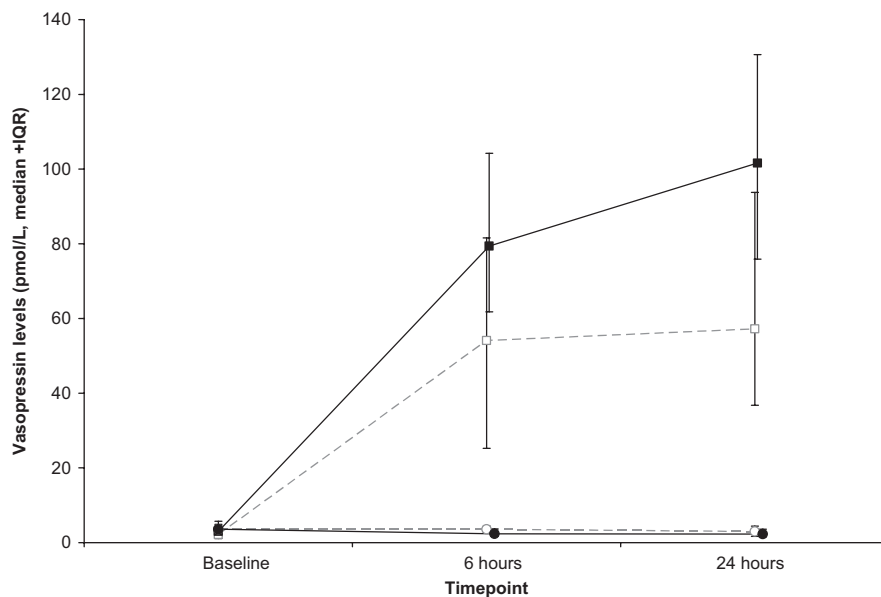


Figure 3. Plasma concentrations of vasopressin were measured by radioimmunoassay in a convenience sample of patients in VASST. Figure 3 shows vasopressin-treated patients who were treated with corticosteroids (black squares) or who were not treated with corticosteroids (open squares). There were no differences between corticosteroid and noncorticosteroid-treated patients at baseline. However, patients who were treated with vasopressin and corticosteroids had significantly higher plasma vasopressin concentrations at 6 hours ( $p = 0.006$ ) and 24 hours ( $0.025$ ) of study drug (vasopressin) infusion compared with patients treated with vasopressin who were not treated with corticosteroids. Figure 3 also shows norepinephrine-treated patients who were treated with corticosteroids (black circles) or who were not treated with corticosteroids (open circles). Plasma vasopressin concentrations were low, did not change during norepinephrine infusion, and there were no differences at baseline, at 6 hours or at 24 hours of study drug (norepinephrine) infusion among norepinephrine-treated patients who were or were not treated with corticosteroids.

(10, 11). Corticosteroids increase vasopressin messenger RNA (7) consistent with our finding that corticosteroids increased vasopressin levels (Fig. 3). Methylprednisolone reverses hypo-responsiveness to vasopressin in endotoxemia (8), which could explain increased responsiveness to vasopressin in patients who

are also receiving corticosteroids. In contrast, Lauand et al (9) found that dexamethasone did not change vasopressin secretion. Kim et al (11) and Kuwahara et al (10) suggested that corticosteroids suppress vasopressin gene expression.

There is a more consistent understanding of the effects of vasopressin on

the corticosteroid axis. Vasopressin potentiates the stimulatory effects of corticotrophin releasing factor because vasopressin binds to the V1b (V3) receptor of pituitary corticotrophs (12–14). Vasopressin-induced increase of adrenocorticotropic hormone is resistant to glucocorticoid feedback because the V1b receptor is not regulated by glucocorticoid levels (12). Overexpression of the V1b receptor increases serum corticosterone (21). One study found that vasopressin infusion did not change ACTH or cortisol levels in septic shock (22).

Strengths of our study include sample size, statistical power, blinded randomization (vasopressin vs. norepinephrine), multicenter design, and strict protocol. Weaknesses are the *post hoc* hypothesis and use of corticosteroids was not randomized, blinded, or controlled. Thus, this study is hypothesis generating—a *post hoc* hypothesis. The results of our study could be different if we used a higher dose of vasopressin (such as 0.066 U/min) (23), and this is a compelling hypothesis for a new study.

## CONCLUSIONS

In conclusion, the combination of low-dose vasopressin and corticosteroids—compared with norepinephrine plus corticosteroids—was associated with a lower mortality in patients who had septic shock. In patients who were treated with vasopressin, patients who were also treated with corticosteroids had higher plasma vasopressin levels during the vasopressin infusion than patients who did not receive corticosteroids. We suggest that a new trial of vasopressin

Table 5. Serious adverse events in patients who had septic shock according to corticosteroid treatment and vasopressin vs. norepinephrine

Variable	Steroid			No Steroid		
	Norepinephrine Group, n (%)	Vasopressin Group, n (%)	p Value <sup>a</sup>	Norepinephrine Group, n (%)	Vasopressin Group, n (%)	p Value <sup>a</sup>
At least one serious adverse event	30 (10.2)	33 (11.1)	0.79	10 (11.2)	8 (11.2)	0.47
Acute myocardial infarction/ischemia	5 (1.7)	8 (2.7)	0.58	2 (2.2)	0 (0.0)	0.22
Cardiac arrest	7 (2.4)	1 (0.3)	0.04	1 (1.1)	2 (2.0)	1.00
Life-threatening arrhythmia	3 (1.0)	5 (1.7)	0.73	3 (3.4)	2 (2.0)	0.66
Acute mesenteric ischemia	10 (3.4)	8 (2.7)	0.64	3 (3.4)	1 (1.0)	0.34
Hyponatremia (serum Na <130 mM)	1 (0.3)	0 (0.0)	0.50	0 (0.0)	1 (1.0)	1.00
Digital ischemia	2 (0.7)	8 (2.7)	0.11	0 (0.0)	0 (0.0)	–
Cerebro-vascular accident	1 (0.3)	0 (0.0)	0.50	0 (0.0)	1 (1.0)	1.00
Other*	1 (0.3)	3 (1.0)	0.62	1 (1.1)	2 (2.0)	1.00

<sup>a</sup>Two-sided p values are based on Fisher's Exact test.

(vs. control) and corticosteroids (vs. placebo) in a factorial design is warranted.

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## APPENDIX

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