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## Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock

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### ABSTRACT

#### BACKGROUND

Vasopressin is commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock, but its effect on mortality is unknown. We hypothesized that low-dose vasopressin as compared with norepinephrine would decrease mortality among patients with septic shock who were being treated with conventional (catecholamine) vasopressors.

#### METHODS

In this multicenter, randomized, double-blind trial, we assigned patients who had septic shock and were receiving a minimum of 5  $\mu\text{g}$  of norepinephrine per minute to receive either low-dose vasopressin (0.01 to 0.03 U per minute) or norepinephrine (5 to 15  $\mu\text{g}$  per minute) in addition to open-label vasopressors. All vasopressor infusions were titrated and tapered according to protocols to maintain a target blood pressure. The primary end point was the mortality rate 28 days after the start of infusions.

#### RESULTS

A total of 778 patients underwent randomization, were infused with the study drug (396 patients received vasopressin, and 382 norepinephrine), and were included in the analysis. There was no significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate (35.4% and 39.3%, respectively;  $P=0.26$ ) or in 90-day mortality (43.9% and 49.6%, respectively;  $P=0.11$ ). There were no significant differences in the overall rates of serious adverse events (10.3% and 10.5%, respectively;  $P=1.00$ ). In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% vs. 35.7%,  $P=0.05$ ); in the stratum of more severe septic shock, there was no significant difference in 28-day mortality (44.0% and 42.5%, respectively;  $P=0.76$ ). A test for heterogeneity between these two study strata was not significant ( $P=0.10$ ).

#### CONCLUSIONS

Low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors. (Current Controlled Trials number, ISRCTN94845869.)

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SEPTIC SHOCK IS THE MOST COMMON cause of death in intensive care units (ICUs)<sup>1,2</sup> and has a mortality rate of 40 to 60%.<sup>2,3</sup> Resuscitation strategies include the administration of intravenous fluids and the use of catecholamines such as norepinephrine, epinephrine, dopamine, and dobutamine.<sup>4,5</sup> Although largely effective in reestablishing minimally acceptable mean arterial pressures to maintain organ perfusion, catecholamines have important adverse effects and may even increase mortality rates.<sup>6</sup> For example, norepinephrine, a potent and commonly used  $\alpha$ -adrenergic agent in cases of septic shock, may decrease cardiac output, oxygen delivery, and blood flow to vulnerable organs despite adequate perfusion pressure.<sup>7</sup>

Vasopressin, an endogenously released peptide hormone, has emerged as an adjunct to catecholamines for patients who have severe septic shock. The rationale for its use is the relative vasopressin deficiency in patients with septic shock and the hypothesis that exogenously administered vasopressin can restore vascular tone and blood pressure, thereby reducing the need for the use of catecholamines.<sup>8-10</sup> Observational studies involving the use of vasopressin infusion rates below 0.1 U per minute in patients with vasodilatory shock have repeatedly shown improved short-term blood-pressure responses.<sup>10-14</sup> However, vasopressin infusion may decrease blood flow in the heart, kidneys, and intestine. Despite the widespread use of vasopressin in clinical practice, only two small randomized trials have evaluated its use in patients who had septic shock.<sup>10,12</sup> Vasopressin increased blood pressure, decreased catecholamine requirements, and improved renal function as compared with a control agent. However, neither of the trials was powered to evaluate mortality, organ dysfunction, or safety.

To address these uncertainties, we conducted a multicenter, randomized, stratified, double-blind trial among patients who had septic shock and were receiving usual care (including catecholamines), to determine whether vasopressin decreased 28-day mortality, as compared with norepinephrine. Our secondary hypothesis was that the beneficial effects of vasopressin would be more pronounced than those of norepinephrine in the subgroup of patients with more severe (as opposed to less severe) septic shock. Therefore, we strati-

fied patients at the time of randomization according to the baseline dose of norepinephrine.

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## METHODS

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This trial was conducted between July 2001 and April 2006 in 27 centers in Canada, Australia, and the United States and was approved by the research ethics boards of all participating institutions. Written informed consent was obtained from all patients, their next of kin, or another surrogate decision maker, as appropriate. The data were collected by the investigators and analyzed by the data management committee. The executive committee vouches for the accuracy and completeness of the data and analysis. The article was written by the writing committee, and the decision to publish was made by the executive committee. Full details of the trial protocol can be found in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org).

### STUDY PATIENTS

Patients older than 16 years of age who had septic shock that was resistant to fluids (as defined by lack of response to 500 ml of normal saline or a requirement for vasopressors [see the Supplementary Appendix]) and low-dose norepinephrine were considered for enrollment. Septic shock was defined by the presence of two or more diagnostic criteria for the systemic inflammatory response syndrome,<sup>15</sup> proven or suspected infection, new dysfunction of at least one organ, and hypotension despite adequate fluid resuscitation (requiring vasopressor support consisting of at least 5  $\mu$ g of norepinephrine or the equivalent per minute [see the Supplementary Appendix] for 6 hours). Exclusion criteria are listed in the Supplementary Appendix.

### TREATMENT ASSIGNMENTS

Treatment with either vasopressin or norepinephrine was assigned by means of a central telephone randomization system accessed by the study pharmacists at the participating institutions. A computer-generated randomization list of variable permuted blocks of 2, 4, and 6 was used for treatment allocation, which was stratified by center and by severity of shock in the hour before randomization (the stratum of less severe septic shock was

defined as treatment with 5 to 14  $\mu\text{g}$  of norepinephrine or the equivalent per minute, and the stratum of more severe septic shock was defined as treatment with 15  $\mu\text{g}$  or more of norepinephrine or the equivalent per minute). Infusions of both study drugs were prepared locally by study pharmacists who were aware of the two treatments. All other clinical staff, investigators, research personnel, patients, and families were unaware of the treatment assignments for the duration of the trial.

#### DRUG INFUSION

Vasopressin (30 U) and norepinephrine (15 mg) were mixed in identical 250-ml intravenous bags of 5% dextrose in water, with final concentrations of 0.12 U of vasopressin per milliliter and 60  $\mu\text{g}$  of norepinephrine per milliliter. The study-drug infusion was started at 5 ml per hour and increased by 2.5 ml per hour every 10 minutes during the first hour to achieve a constant target rate of 15 ml per hour. Thus, the blinded vasopressin infusion was started at 0.01 U per minute and titrated to a maximum of 0.03 U per minute, whereas the blinded norepinephrine infusion was started at 5  $\mu\text{g}$  per minute and titrated to a maximum of 15  $\mu\text{g}$  per minute.

During the initiation and titration of the study drug, the bedside nurse also titrated open-label vasopressors to maintain a constant target mean arterial pressure. An initial target mean arterial pressure of 65 to 75 mm Hg was recommended; however, the attending ICU physician could modify the target blood pressure of each patient.

Open-label vasopressors were increased only if the target mean arterial pressure was not reached on maximal study-drug infusion. Tapering of open-label vasopressors was permitted only when the target mean arterial pressure had been reached during the study-drug infusion. Tapering of the study drug was commenced only when the target mean arterial pressure had been maintained for 8 hours without any open-label vasopressors. Infusion of the study drug was continued at 15 ml per hour until the patient died, a serious adverse event occurred, or the patient's condition improved to the extent that open-label vasopressors were no longer required. Neither crossover to the other group nor open-label vasopressin was permitted.

The study-drug infusion was discontinued or

interrupted if any of the following predetermined serious adverse events occurred: acute ST-segment elevation confirmed by a 12-lead electrocardiogram, serious or life-threatening (hemodynamically unstable) cardiac arrhythmias, acute mesenteric ischemia, digital ischemia, or hyponatremia (serum sodium level,  $<130$  mmol per liter). If the clinical team noted an adverse event that they considered to be related to the study drug, then the study drug was discontinued for at least 8 hours and a serious adverse event was reported. The study drug could be restarted if, in the judgment of the investigator or attending physician, the adverse event had been treated, the condition had been reversed, and the event was not thought to have been a result of the study drug or study protocol.

If vasopressor support was required during the same admission to the ICU after a patient had been weaned from the study drug, the study drug was preferentially reinfused, as long as no exclusion criteria were met. In a subgroup of patients at six of the participating institutions, plasma was collected for measurement of circulating vasopressin levels (see the Supplementary Appendix).

#### END POINTS

The primary outcome was death from any cause and was assessed 28 days after the start of infusions. Secondary outcomes included 90-day mortality; days alive and free of organ dysfunction during the first 28 days according to the Brussels criteria<sup>16</sup> (see the Supplementary Appendix); days alive and free of vasopressor use, mechanical ventilation, or renal replacement therapy; days alive and free of the systemic inflammatory response syndrome, defined as freedom from two or more of the four diagnostic criteria for the systemic inflammatory response syndrome; days alive and free of corticosteroid use; and length of stay in the ICU and hospital. We also evaluated rates of serious adverse events.

#### STATISTICAL ANALYSIS

We calculated that 776 patients were required for enrollment, randomization, and receipt of the study drug in order to detect an absolute 10% difference in mortality, assuming a mortality rate of 60% in the norepinephrine group and a two-sided alpha error of 0.05 and a power of 80%. An independent

data and safety monitoring committee evaluated two preplanned interim analyses, after 194 patients had been enrolled and after 388 patients had been enrolled. An O'Brien–Fleming approach was used for sequential stopping rules for safety and efficacy according to the Lan–DeMets method.<sup>17</sup> After both interim analyses, the data and safety monitoring committee recommended that the study be continued without protocol modification.

Midway through the trial, the executive committee, unaware of all data and in conference with the data and safety monitoring committee, determined that patients who had undergone randomization but had never received an infusion would not be included in the primary analysis, since their omission would be equally distributed between groups, would be unrelated to treatment assignment, and would not bias outcome ascertainment.<sup>18</sup> We increased the total number of patients enrolled to maintain the target sample size after the removal of such patients from the analysis.

The primary analysis, which compared 28-day mortality between the two treatment groups, was performed with the use of an unadjusted chi-square test, and all patients were assessed according to the treatment received and to the treatment group assigned at randomization. Results are presented as absolute and relative risks and 95% confidence intervals. Kaplan–Meier curves for the estimated probability of survival in the two treatment groups as a function of time from enrollment in the study were compared with the use of the log-rank test.

Because of the complex nature of septic shock and to account for any imbalances between the two treatment groups at baseline, a logistic-regression procedure and significant covariates that predicted outcomes were used to adjust raw values for 28-day mortality. Age, illness severity (score on the Acute Physiology and Chronic Health Evaluation [APACHE II] at baseline), serious coexisting conditions, and other baseline covariates that predicted outcome (at a threshold P value of 0.20) were entered into the model. Results are presented as odds ratios and 95% confidence intervals. We used parametric procedures (independent t-test), nonparametric procedures (Wilcoxon rank-sum test), or Fisher's exact test to compare all secondary outcomes.

Patients were also assessed according to the a priori strata of more severe or less severe septic shock (as defined by the dose of norepinephrine)

as well as in several exploratory analyses of shock severity defined by post hoc criteria. The treatment effect within each subgroup was assessed according to the within-stratum analysis, with the use of the chi-square test. We also used logistic-regression analysis to test for an interaction between stratum and treatment in order to determine whether there was a differential effect on mortality.

The data analyst and investigators remained unaware of the treatment assignments while undertaking the final analyses. Analysis was conducted with the use of SAS software (version 9.1.3), and all P values were two-sided.

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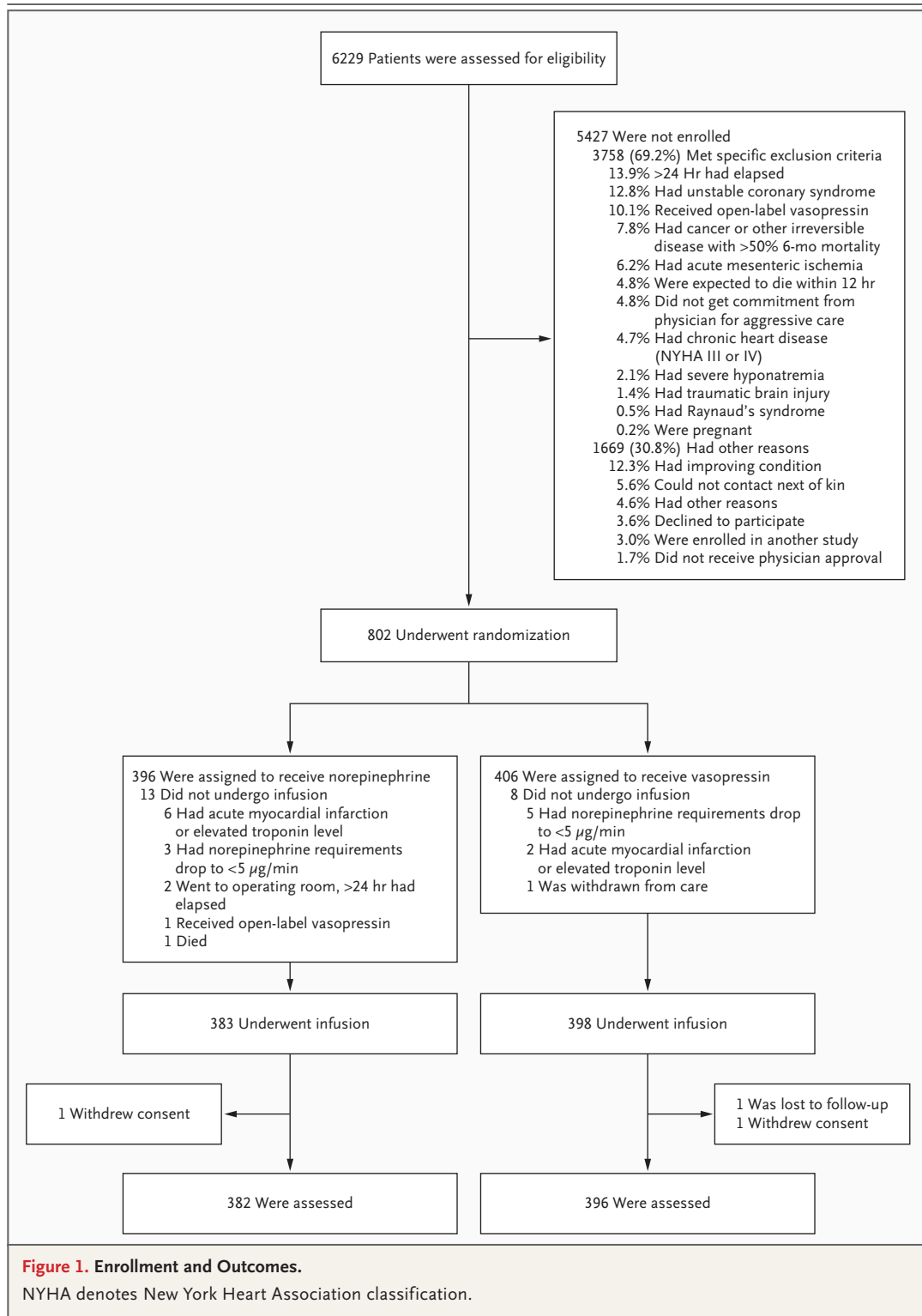
## RESULTS

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Of 6229 screened patients, 802 underwent randomization after providing informed consent (Fig. 1). Of these 802 patients, 2 withdrew consent after infusion of the study drug and 21 did not receive the infusion for various reasons. In addition, one patient was lost to follow-up before day 28. Thus 779 patients underwent randomization and infusion of the study drug, and 778 were included in the final primary analysis: 396 in the vasopressin group and 382 in the norepinephrine group (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. Enrolled patients were severely ill, as indicated by the APACHE II scores,<sup>19</sup> by the proportion with new organ dysfunction, by the serum lactate levels, and by the norepinephrine infusion rates at study entry.

Blood pressure in the two treatment groups was similar throughout the study, whereas the heart rate was significantly lower in the vasopressin group than in the norepinephrine group during the first 4 days of treatment ( $P < 0.001$ ) (Fig. 1 in the Supplementary Appendix). The difference in the mean infusion rates of the study drug between treatment groups during the first 5 days was within 2 ml per hour. The rate of norepinephrine infusion was significantly lower in the vasopressin group than in the norepinephrine group during the first 4 days ( $P < 0.001$ ) (Fig. 2 in the Supplementary Appendix).

There was no significant difference in the primary outcome (rate of death from any cause, assessed 28 days after the start of infusions), between the vasopressin group and the norepinephrine group (35.4% and 39.3%, respectively;  $P = 0.26$ ; 95% confidence interval [CI] for absolute risk re-



duction in the vasopressin group, -2.9 to 10.7%) (Table 2 and Fig. 2). Similarly, there was no significant difference in mortality at 90 days (43.9% and 49.6%, respectively; P=0.11; 95% CI for abso-

lute risk reduction, -1.3 to 12.8%) or in rates of organ dysfunction (Table 2). The results remained nonsignificant after multivariate logistic-regression analysis (odds ratio for death in the vasopress-

**Table 1. Demographic and Baseline Characteristics of the Patients.\***

| Characteristic                        | Norepinephrine Group<br>(N=382) | Vasopressin Group<br>(N=397) | P Value |
|---------------------------------------|---------------------------------|------------------------------|---------|
| Age — yr                              | 61.8±16                         | 59.3±16.4                    | 0.03    |
| Male sex — no. (%)                    | 229 (59.9)                      | 246 (62.0)                   | 0.56    |
| Recent surgical history — no. (%)     | 132 (34.6)                      | 151 (38.0)                   | 0.31    |
| Elective                              | 8 (2.1)                         | 6 (1.5)                      |         |
| Emergency                             | 124 (32.5)                      | 145 (36.5)                   |         |
| APACHE II score                       | 27.1±6.9                        | 27.0±7.7                     | 0.84    |
| White race — no. (%)†                 | 320 (83.8)                      | 336 (84.6)                   | 0.97    |
| Preexisting conditions — no. (%)      |                                 |                              |         |
| Ischemic heart disease                | 65 (17.0)                       | 68 (17.1)                    | 0.62    |
| Congestive heart failure              | 30 (7.9)                        | 28 (7.1)                     | 0.56    |
| Chronic obstructive pulmonary disease | 72 (18.8)                       | 55 (13.9)                    | 0.11    |
| Chronic renal failure                 | 48 (12.6)                       | 40 (10.1)                    | 0.34    |
| Diabetes                              | 88 (23.0)                       | 77 (19.4)                    | 0.29    |
| Liver disease                         | 36 (9.4)                        | 52 (13.1)                    | 0.16    |
| Alcoholism                            | 53 (13.9)                       | 55 (13.9)                    | 0.62    |
| Injection-drug abuse                  | 14 (3.7)                        | 20 (5.0)                     | 0.40    |
| Cancer                                | 104 (27.2)                      | 85 (21.4)                    | 0.11    |
| Compromised immune system             | 72 (18.8)                       | 67 (16.9)                    | 0.48    |
| Solid-organ transplant                | 17 (4.5)                        | 14 (3.5)                     | 0.50    |
| Corticosteroid use                    | 86 (22.5)                       | 82 (20.7)                    | 0.51    |
| Recent trauma                         | 16 (4.2)                        | 23 (5.8)                     | 0.30    |
| New organ failure — no. (%)           |                                 |                              |         |
| Cardiovascular                        | 382 (100)                       | 397 (100)                    | 1.00    |
| Respiratory                           | 341 (89.3)                      | 342 (86.1)                   | 0.15    |
| Renal                                 | 258 (67.5)                      | 264 (66.5)                   | 0.68    |
| Hematologic and coagulation           | 84 (22.0)                       | 118 (29.7)                   | 0.02    |
| Neurologic                            | 89 (23.3)                       | 101 (25.4)                   | 0.48    |
| No. of organ dysfunctions             | 3.4±1.1                         | 3.5±1.1                      | 0.04    |
| Source of infection — no. (%)         |                                 |                              | 0.77    |
| Lung                                  | 165 (43.2)                      | 162 (40.8)                   |         |
| Abdomen                               | 100 (26.2)                      | 111 (28.0)                   |         |
| Other‡                                | 117 (30.6)                      | 124 (31.2)                   |         |
| Pathogen type in cultures — no. (%)   |                                 |                              | 0.19    |
| Gram-positive alone                   | 59 (15.4)                       | 80 (20.2)                    |         |
| Gram-negative alone                   | 43 (11.3)                       | 40 (10.1)                    |         |
| Mixed organisms                       | 139 (36.4)                      | 143 (36.0)                   |         |
| Other                                 | 51 (13.4)                       | 62 (15.6)                    |         |
| No pathogen                           | 90 (23.6)                       | 72 (18.1)                    |         |
| Hemodynamic variables                 |                                 |                              |         |
| Systolic blood pressure — mm Hg       | 110±17                          | 108±17                       | 0.10    |
| Mean arterial pressure — mm Hg        | 73±10                           | 72±9                         | 0.23    |
| Arterial pH                           | 7.31±0.1                        | 7.32±0.1                     | 0.71    |
| Serum lactate level — mmol/liter      | 3.5±3.0                         | 3.5±3.2                      | 0.96    |

**Table 1. (Continued.)**

| Characteristic   | Norepinephrine Group<br>(N=382)   | Vasopressin Group<br>(N=397)      | P Value |
|--|-----------------------------------|-----------------------------------|---------|
| Vasoactive drug dosage at randomization§   |                                   |                                   |         |
| Norepinephrine — $\mu\text{g}/\text{min}$ ( $\mu\text{g}/\text{kg}/\text{min}$ ) | 20.7 $\pm$ 18.1 (0.28 $\pm$ 0.26) | 20.7 $\pm$ 22.1 (0.26 $\pm$ 0.27) | 0.97    |
| Epinephrine — $\mu\text{g}/\text{min}$ ( $\mu\text{g}/\text{kg}/\text{min}$ )    | 8.6 $\pm$ 9.4 (0.12 $\pm$ 0.15)   | 14.6 $\pm$ 16.9 (0.20 $\pm$ 0.29) | 0.12    |
| Dopamine — $\mu\text{g}/\text{kg}/\text{min}$                                    | 7.3 $\pm$ 5.3                     | 7.6 $\pm$ 6.4                     | 0.88    |
| Dobutamine — $\mu\text{g}/\text{kg}/\text{min}$                                  | 5.1 $\pm$ 3.7                     | 6.4 $\pm$ 5.2                     | 0.18    |
| Milrinone — $\mu\text{g}/\text{kg}/\text{min}$                                   | 0.4 $\pm$ 0.3                     | 0.3 $\pm$ 0.1                     | 0.23    |
| Phenylephrine — $\mu\text{g}/\text{min}$ ( $\mu\text{g}/\text{kg}/\text{min}$ )  | 151 $\pm$ 74 (2.03 $\pm$ 1.17)    | 157 $\pm$ 90 (2.04 $\pm$ 1.31)    | 0.61    |
| Vasoactive drug infusions — no. (%)  |                                   |                                   |         |
| Norepinephrine alone   | 222 (58.1)                        | 224 (56.4)                        | 0.63    |
| No norepinephrine  | 53 (13.9)                         | 53 (13.4)                         | 0.83    |
| Two or more vasopressors   | 111 (29.1)                        | 124 (31.2)                        | 0.51    |
| Other therapy for sepsis — no. (%)   |                                   |                                   |         |
| Corticosteroids  | 293 (76.7)                        | 296 (74.6)                        | 0.49    |
| Activated protein C  | 56 (14.7)                         | 61 (15.4)                         | 0.78    |
| Baseline tidal volume — ml/kg  | 7.4 $\pm$ 2.5                     | 7.2 $\pm$ 2.5                     | 0.43    |
| Time from meeting inclusion criteria to study-drug infusion — hr                 | 11.5 $\pm$ 9.4                    | 11.9 $\pm$ 8.9                    | 0.57    |

\* Plus-minus values are means  $\pm$ SD. APACHE II denotes Acute Physiology and Chronic Health Evaluation II.<sup>19</sup>

† Race was determined by the local study coordinators.

‡ Other sources of infection included blood, skin, central nervous system, bones and joints, cardiac system, and reproductive organs.

§ For norepinephrine, there were 329 patients in the norepinephrine group and 344 in the vasopressin group. For epinephrine, there were 23 patients in the norepinephrine group and 27 in the vasopressin group. For dopamine, there were 28 patients in the norepinephrine group and 26 in the vasopressin group. For dobutamine, there were 41 patients in the norepinephrine group and 48 in the vasopressin group. For milrinone, there were 10 patients in the norepinephrine group and 13 in the vasopressin group. For phenylephrine, there were 71 patients in the norepinephrine group and 85 in the vasopressin group.

sin group at 28 days, 0.88 [95% CI, 0.62 to 1.26]; odds ratio for death at 90 days, 0.81 [95% CI, 0.57 to 1.16]).

There were no significant differences in the overall rates or specific categories of serious adverse events between the vasopressin and norepinephrine groups (overall rates, 10.3% and 10.5%, respectively;  $P=1.00$ ) (Table 3). There was a trend toward a higher rate of cardiac arrest in the norepinephrine group than in the vasopressin group (2.1% vs. 0.8%,  $P=0.14$ ) and a trend toward a higher rate of digital ischemia in the vasopressin group than in the norepinephrine group (2.0% vs. 0.5%,  $P=0.11$ ).

In the subgroup of patients in whom plasma vasopressin levels were measured, the levels were extremely low at baseline (median, 3.2 pmol per liter; interquartile range, 1.7 to 4.9). These levels did not change in the norepinephrine group. Infusion of low-dose vasopressin increased vasopressin levels to medians of 73.6 pmol per liter (inter-

quartile range, 58.6 to 94.7) at 6 hours and 98.0 pmol per liter (interquartile range, 67.1 to 127.8) at 24 hours (Fig. 3 in the Supplementary Appendix).

Baseline characteristics of the patients in the stratum of more severe septic shock and those in the stratum of less severe septic shock are presented in the Supplementary Appendix. Among patients who had less severe septic shock (an infusion of 5 to 14  $\mu\text{g}$  of norepinephrine per minute at randomization), there were trends in favor of the vasopressin group with respect to both 28-day and 90-day mortality (Table 4). In contrast, there were no significant differences in mortality between the vasopressin and norepinephrine groups in the stratum of more severe septic shock. However, the test for the interaction between the treatment assignment and the severity-of-shock subgroup was not significant ( $P=0.10$ ). We performed several additional post hoc analyses of the results stratified according to different indicators of illness severity (Table 3 of the Supplementary

**Table 2. Analysis of the Rates and Risks of Death from Any Cause and Secondary Outcomes.\***

| Variable   | Norepinephrine Group<br>(N=382)<br><i>no./total no. (%)</i> | Vasopressin Group<br>(N=396)<br><i>no./total no. (%)</i> | P Value† | Absolute Risk Reduction<br>(95% CI)‡<br>% | Relative Risk<br>(95% CI)§ | Adjusted Odds Ratio¶ |
|--|---|--|----------|---|----------------------------|----------------------|
| <b>Patients who underwent randomization and infusion</b> |   |  |          |   |                            |                      |
| 28-day mortality   | 150/382 (39.3)  | 140/396 (35.4)   | 0.26     | 3.9 (-2.9 to 10.7)                        | 0.90 (0.75 to 1.08)        | 0.88 (0.62 to 1.26)  |
| 90-day mortality   | 188/379 (49.6)  | 172/392 (43.9)   | 0.11     | 5.7 (-1.3 to 12.8)                        | 0.88 (0.76 to 1.03)        | 0.81 (0.57 to 1.16)  |
| <b>Patients who underwent randomization</b>              |   |  |          |   |                            |                      |
| 28-day mortality   | 154/395 (39.0)  | 144/404 (35.6)   | 0.33     | 3.3 (-3.4 to 10.1)                        | 0.91 (0.76 to 1.09)        |                      |
| 90-day mortality   | 194/392 (49.5)  | 177/400 (44.2)   | 0.14     | 5.2 (-1.7 to 12.2)                        | 0.89 (0.77 to 1.04)        |                      |
| <i>median (interquartile range)</i>                      |   |  |          |   |                            |                      |
| <b>Days alive  </b>                                      |   |  |          |   |                            |                      |
| Free of organ dysfunction                                |   |  |          |   |                            |                      |
| Cardiovascular   | 17 (0–24)   | 19 (0–24)  | 0.58     |   |                            |                      |
| Vasopressor use**  | 17 (0–24)   | 19 (0–24)  | 0.61     |   |                            |                      |
| Respiratory  | 2 (0–14)  | 3.5 (0–16)   | 0.15     |   |                            |                      |
| Ventilation††  | 6 (0–20)  | 8.5 (0–20)   | 0.24     |   |                            |                      |
| Renal  | 18.5 (3–28)   | 21.5 (4–28)  | 0.54     |   |                            |                      |
| Renal-replacement therapy                                | 23 (5–28)   | 25 (6–28)  | 0.64     |   |                            |                      |
| Hepatic  | 24.5 (3–28)   | 25 (5–28)  | 0.80     |   |                            |                      |
| Hematologic  | 23 (3–28)   | 24 (5–28)  | 0.48     |   |                            |                      |
| Neurologic   | 15 (0–24)   | 15 (0–24)  | 0.57     |   |                            |                      |
| Free of any organ failure                                | 0 (0–6)   | 0 (0–9)  | 0.14     |   |                            |                      |
| Free of the systemic inflammatory response syndrome‡‡    | 6 (0–15)  | 6 (0–18)   | 0.21     |   |                            |                      |
| Free of corticosteroid use                               | 13.5 (1–24)   | 16 (1–25)  | 0.33     |   |                            |                      |
| <b>Length of stay (days)</b>                             |   |  |          |   |                            |                      |
| In ICU   | 16 (8–32)   | 15 (7–29)  | 0.14     |   |                            |                      |
| In hospital  | 26 (15–53)  | 27 (13–52)   | 0.23     |   |                            |                      |

\* Patients were analyzed in the treatment group to which they were assigned at randomization.

† Two-sided P values are based on Pearson's chi-square test.

‡ The absolute risk reduction is the mortality rate in the norepinephrine group minus the mortality rate in the vasopressin group.

§ The relative risk is the mortality rate in the vasopressin group divided by the mortality rate in the norepinephrine group.

¶ Multivariate logistic-regression analysis incorporated all significant covariates from Table 1. Baseline information was not available on the patients who underwent randomization but did not undergo infusion. Therefore, an adjusted analysis of the randomized, intention-to-treat population was not possible.

|| Organ dysfunction for each organ system was considered to be present during each 24-hour period if there was evidence of moderate, severe, or extreme organ dysfunction according to the Brussels criteria<sup>16</sup> (see the Supplementary Appendix). A low score indicates more severe organ dysfunction and fewer days alive while free of organ dysfunction. P values are based on the Wilcoxon rank-sum test.

\*\* Vasopressor use was defined as 5 µg or more of dopamine per kilogram per minute or any dose of norepinephrine, epinephrine, or phenylephrine.

†† Ventilation was defined as intubation and positive-pressure ventilation.

‡‡ Freedom from the systemic inflammatory response syndrome was defined as freedom from two or more of the four diagnostic criteria.

Appendix). For most of these analyses, there was no evidence of a significant interaction between illness severity and vasopressin effect. Two of the interaction analyses (stratification according to quartile of lactate level and according to number of vasopressors at baseline) yielded moderately significant P values (P=0.04 for both), suggesting a possible advantage of vasopressin in patients



with less severe shock (Table 3 in the Supplementary Appendix).

DISCUSSION

In this multicenter, randomized, double-blind trial of low-dose vasopressin as compared with norepinephrine in patients with septic shock, we were not able to demonstrate any significant difference in the 28-day mortality rate (35.4% in the vasopressin group vs. 39.3% in the norepinephrine group,  $P=0.26$ ). We were also unable to demonstrate any significant difference between the two study groups in 90-day mortality or the rate of organ dysfunction. There was no difference in the rates of serious adverse events between the vasopressin and norepinephrine groups. Infusions of low-dose vasopressin (0.03 U per minute) increased plasma vasopressin levels to approximately 70 to 100 pmol per liter from extremely low baseline vasopressin levels (median, 3.2 pmol per liter). Consistent with at least 14 previous trials in humans<sup>10-14,20-28</sup> of low-dose vasopressin ( $\leq 0.1$  U per minute), vasopressin infusion allowed a rapid decrease in the total norepinephrine dose while maintaining mean arterial pressure.<sup>10-12,29</sup>

Our study was prospectively powered to detect an absolute difference in mortality of 10% from an expected 60%. However, the observed mortality rates in both the vasopressin and norepinephrine groups were considerably lower than those in previous studies, perhaps because of overall improvements in the care of patients who have septic shock. Nonetheless, our data exclude with 95% confidence a harm associated with the use of vasopressin that was greater than 2.9% or a benefit that was greater than 10.7%.

The overall rates of serious adverse events were approximately 10% each in the vasopressin and norepinephrine groups. Previous studies raised the possibility that vasopressin infusion may increase the incidence of cardiac arrest.<sup>29</sup> In contrast, we found that of 11 cardiac arrests reported in this study, 8 occurred in the norepinephrine group and 3 occurred in the vasopressin group. Our selection of a low dose of vasopressin (0.03 U per minute) and careful exclusion of patients who had acute coronary syndromes or severe heart failure could account for the lack of adverse cardiovascular effects of vasopressin infusion. If vasopressin becomes routine therapy and is given at higher doses or to patients with septic shock who have coexisting heart disease, the adverse reac-

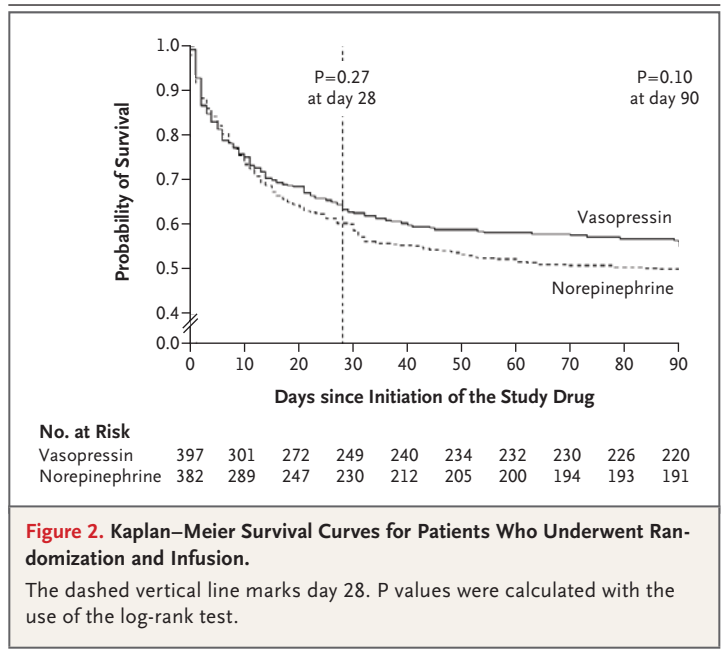


Figure 2. Kaplan-Meier Survival Curves for Patients Who Underwent Randomization and Infusion.

The dashed vertical line marks day 28. P values were calculated with the use of the log-rank test.

Table 3. Serious Adverse Events in Patients Who Had Septic Shock.

| Variable                                | Norepinephrine Group (N=382) | Vasopressin Group (N=396) | P Value* |
|---|------------------------------|---------------------------|----------|
|   | no. (%)                      |                           |          |
| At least one serious adverse event      | 40 (10.5)                    | 41 (10.3)                 | 1.00     |
| Acute myocardial infarction or ischemia | 7 (1.8)                      | 8 (2.0)                   | 1.00     |
| Cardiac arrest                          | 8 (2.1)                      | 3 (0.8)                   | 0.14     |
| Life-threatening arrhythmia             | 6 (1.6)                      | 8 (2.0)                   | 0.79     |
| Acute mesenteric ischemia               | 13 (3.4)                     | 9 (2.3)                   | 0.39     |
| Hyponatremia†                           | 1 (0.3)                      | 1 (0.3)                   | 1.00     |
| Digital ischemia                        | 2 (0.5)                      | 8 (2.0)                   | 0.11     |
| Cerebrovascular accident                | 1 (0.3)                      | 1 (0.3)                   | 1.00     |
| Other‡                                  | 2 (0.5)                      | 5 (1.3)                   | 0.45     |

\* Two-sided P values are based on Fisher's exact test.

† Hyponatremia was defined as a serum sodium level of less than 130 mmol per liter.

‡ Other events include acute hepatitis, agranulocytosis, pulmonary embolism, seizures, drug error, and two cases of drug extravasation from the central venous catheter.

tions to vasopressin could be increased. Other reported adverse effects of vasopressin and norepinephrine include decreased cardiac output,<sup>11,14,29</sup> mesenteric ischemia,<sup>21,30</sup> hyponatremia (with vasopressin only), skin necrosis,<sup>31</sup> and digital ischemia.<sup>32</sup> More patients in the vasopressin group than in the norepinephrine group had digital ische-

**Table 4. Rates and Risks of Death from Any Cause According to the Severity of Shock.\***

| Stratum                  | Norepinephrine Group<br>no./total no. (%) | Vasopressin Group<br>no./total no. (%) | P Value† | Absolute Risk Reduction<br>(95% CI)<br>% | Relative Risk<br>(95% CI) |
|--------------------------|---|--|----------|--|---------------------------|
| More severe septic shock |   |  |          |  |                           |
| 28-day mortality         | 85/200 (42.5)                             | 88/200 (44.0)                          | 0.76     | -1.5 (-11.2 to 8.2)                      | 1.04 (0.83 to 1.3)        |
| 90-day mortality         | 105/199 (52.8)                            | 103/199 (51.8)                         | 0.84     | 1.0 (-8.8 to 10.8)                       | 0.98 (0.81 to 1.18)       |
| Less severe septic shock |   |  |          |  |                           |
| 28-day mortality         | 65/182 (35.7)                             | 52/196 (26.5)                          | 0.05     | 9.2 (-0.1 to 18.5)                       | 0.74 (0.55 to 1.01)       |
| 90-day mortality         | 83/180 (46.1)                             | 69/193 (35.8)                          | 0.04     | 10.4 (0.4 to 20.3)                       | 0.78 (0.61 to 0.99)       |

\* Patients with more severe septic shock were defined as those who required at least 15  $\mu\text{g}$  of norepinephrine per minute or the equivalent at the time of randomization. Those with less severe septic shock were defined as those who required 5 to 14  $\mu\text{g}$  of norepinephrine per minute or the equivalent at the time of randomization.

† Two-sided P values are based on Pearson's chi-square test.

mia; one patient in the vasopressin group required surgical intervention.

Our secondary hypothesis was that the beneficial effects of vasopressin as compared with norepinephrine would be more pronounced in the subgroup of patients with more severe septic shock. No significant interaction between treatment group and shock-severity subgroup (as defined a priori) was shown. Some of the analyses we performed suggested that vasopressin may be more beneficial in patients with less severe septic shock. However, the statistical significance of these observations is uncertain, especially because of the many statistical tests performed, and this finding should be considered only as a hypothesis-generating concept to be tested in future trials.<sup>33</sup>

Several limitations of our trial should be mentioned. The vasopressin was infused over a set range of doses, and we did not measure vasopressin levels as a guide to the dose or the duration of infusion. In addition, in this trial the mean arterial pressure at baseline was 72 to 73 mm Hg, essentially making this a study of the effects of low-dose vasopressin as a "catecholamine-sparing

drug," not an evaluation of vasopressin in patients with catecholamine-unresponsive refractory shock. The mean time from meeting the criteria for study entry to infusion of the study drug (12 hours) was greater than the period that Rivers and colleagues<sup>4</sup> identified as being important in early goal-directed therapy (6 hours), which may be one reason that we did not find a benefit of vasopressin as compared with norepinephrine.

In summary, we evaluated the effect of low-dose vasopressin (0.03 U per minute) when used in conjunction with catecholamine vasopressors in patients with septic shock. We did not find a significant reduction in mortality rates with vasopressin.

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Drs. Russell, Walley, and Gordon report serving as officers and holding stock in Sirius Genomics, which has submitted a patent, owned by the University of British Columbia and licensed to Sirius Genomics, that is related to the genetics of vasopressin. The University of British Columbia has also submitted a patent related to the use of vasopressin in septic shock. Drs. Russell, Walley, and Gordon report being inventors on this patent. Drs. Russell and Walley report receiving consulting fees from Ferring, which manufactures vasopressin. Dr. Russell reports receiving grant support from Sirius Genomics, Novartis, and Eli Lilly; and Dr. Wally, from Sirius Genomics. No other potential conflict of interest relevant to this article was reported.

#### APPENDIX

The following persons and institutions participated in the Vasopressin and Septic Shock Trial (VASST): **Writing Committee** — J.A. Russell (chair), K.R. Walley, A.C. Gordon, C. Holmes, J.T. Granton, P.C. Hébert, D.J. Cooper, S. Mehta, J. Singer, D.J. Cook, J.J. Presneill, M.M. Storms; **Executive Committee** — J.A. Russell (chair), K.R. Walley, C.L. Holmes, J.T. Granton, P.C. Hébert, D.J. Cooper, S. Mehta, J. Singer, A.C. Gordon, M.M. Storms (project coordinator), S. Jones (administrative assistant); **Management Committee** — J.A. Russell (chair), M.M. Storms (project coordinator), K.R. Walley, C.L. Holmes, J. Singer, A.C. Gordon, S. Jones (administrative assistant); **Data Safety and Monitoring Board** — G.R. Bernard (chair), A.S. Slutsky, G.A. Wells; **Canadian Institutes of Health Research** — A. Gasparini; **Data Management** — J. Singer, B. Savage, D. Ayers, R. Woods, K. Wu, M. Maralit; **Monitoring** — L. Smith, K. Foley, A. Suri, M. Steinberg, B. Howe, P. Galt, A. Higgins, M.M. Storms; **Laboratory** — M.E. LeBlanc, A.M. Sutherland, A. Sham, A. McLeod; **Clinical Centers and Investigators: Canada — British Columbia: St. Paul's Hospital** — J.A. Russell, K.R. Walley, D.R. Dorscheid, M. Hameed, L. Lazosky, S. Helderweirt, K. Foley, C. Honeyman, T. Terins; **Vancouver General Hospital** — D. Chittock, J. Ronco, L. Smith, S. Logie; **Royal Jubilee**

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