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## Vasopressin in Septic Shock

**TO THE EDITOR:** The results of the Vasopressin and Septic Shock Trial (VASST), reported by Russell et al. (Feb. 28 issue),<sup>1</sup> do not fully support the conclusion that “low-dose vasopressin did not reduce mortality.” The secondary hypothesis that “the beneficial effects of vasopressin would be more pronounced . . . in the subgroup of patients with more severe (as opposed to less severe) septic shock” was clearly refuted. However, in the vasopressin-treated patients with less severe shock, the 25.8% relative reduction in 28-day mortality is both striking and significant. Since the subgroup stratification was done prospectively, this result appears to be more than merely “hypothesis generating.” Moreover, rather than being surprising or paradoxical,<sup>2</sup> these results are consistent with our recent findings in isolated arteries, in which the “beneficial” synergistic effect of low-dose vasopressin (on norepinephrine responsiveness) was preserved in conditions mimicking less severe septic shock but was eliminated in a model of more severe shock.<sup>3</sup> Accordingly, survival effects in the subgroups of patients in VASST parallel our results in vessels and appear to support our hypothesis that “larger amounts of vasopressin may be needed in patients with more severe septic shock.” That hypothesis should be considered in future clinical trials.

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**TO THE EDITOR:** We believe that the study population in VASST was unlikely to benefit from vasopressin. The rationale for vasopressin therapy in

vasodilatory shock is to reduce high, potentially toxic, catecholamine dosages to ranges with a reasonable benefit–risk ratio. A cohort study indicated that 0.6  $\mu\text{g}$  of norepinephrine per kilogram of body weight per minute might constitute such a critical limit.<sup>1</sup> Since the mean norepinephrine dose at randomization in VASST was 0.27  $\mu\text{g}$  per kilogram per minute, the risk of catecholamine toxicity may have been low, and thus, few advantages could be expected from lowering catecholamine dosages. In contrast, patients more likely to benefit from vasopressin-mediated decreases in catecholamine dosages — such as severely sick patients who were expected to die within 12 hours, patients in unstable condition who were receiving vasopressin before study enrollment, and patients with high-risk cardiac disease who were sensitive to catecholamines — were excluded from the trial. According to one report, 0.067 IU of vasopressin per minute resulted in better hemodynamic stabilization than 0.033 IU per minute.<sup>2</sup> This could explain why no survival benefit was achieved with 0.01 to 0.03 IU of vasopressin per minute in patients requiring more than 15  $\mu\text{g}$  of norepinephrine per minute.

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**TO THE EDITOR:** A mortality-end-point study of vasopressin in patients with septic shock has been of interest to us since our finding that such patients are vasopressin-deficient.<sup>1-3</sup> However, the study by Russell et al. showed no benefit of vasopressin. Negative studies discourage further research, but since it is likely that vasopressin was in fact beneficial in some patients, we believe that there is a need for additional trials. As the authors

recognized, the overall death rate at 28 days was nowhere near the 60% rate that was anticipated in the control group; thus, the study was underpowered. A beneficial effect of vasopressin in one of the strata was discounted because the test result for heterogeneity between the two strata was not significant, but this test has very low power.<sup>4</sup> Pressor catecholamines are routine therapy for septic shock, but their efficacy has never been tested in a well-designed trial. Thus, we suggest that the best design for a future trial would be an assessment of 90-day mortality with the use of norepinephrine alone, vasopressin alone, and the two combined.

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**TO THE EDITOR:** Hyponatremia is a frequent electrolyte abnormality in critical care units. Its incidence is estimated to be more than 10%.<sup>1,2</sup> However, in the study by Russell et al., hyponatremia occurred in only 0.3% of patients with septic shock. The patients had several factors that would predispose them to hyponatremia — particularly, effective circulating volume depletion due to septic shock, hypotension, and cardiac failure. In addition, the vasopressin-treated group had extremely high vasopressin (antidiuretic hormone) levels, at 70 to 100 pmol per liter, which if unopposed would lead to severe hyponatremia. This apparent discrepancy requires an explanation by the authors. A very effective algorithm for preventing hyponatremia was evidently used. This algorithm may have included measures that had a bearing on the ultimate outcome of the study (details of fluid management, vasopressin-receptor antagonists, and so forth) and should be disclosed. The authors' approach to the prevention of hyponatremia could provide further clues that might help explain the fascinating outcome of the study, but it would also be of significant clinical interest

to providers managing hyponatremia in the critical care setting worldwide.

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**THE AUTHORS REPLY:** We agree with Boyle and Leone that the effects of vasopressin in patients who had less severe septic shock were striking. These authors' studies of vascular responsiveness provide one biologic explanation for a beneficial response to vasopressin in patients with less severe shock, which was eliminated in patients who had more severe shock. We agree that the use of a higher dose of vasopressin in patients with more severe shock should be evaluated in future studies.

Dünser and colleagues suggest that the dose of norepinephrine at baseline (5  $\mu$ g per kilogram per minute) in VASST was too low. However, that norepinephrine dose did identify patients who had profound vasopressin deficiency. Dünser and colleagues have reported "better hemodynamic stabilization" with the use of 0.067 IU per minute as compared with 0.033 IU per minute (increasing mean arterial pressures to 75 to 80 mm Hg), but they also found new adverse effects of vasopressin (increased bilirubin levels, elevated aminotransferase levels, and thrombocytopenia).<sup>1,2</sup> Our choice of the vasopressin dose of 0.03 IU per minute in VASST was based in part on finding an association between an increased risk of cardiac arrest and vasopressin doses greater than 0.04 IU per minute.<sup>3</sup> VASST showed that this low-dose infusion resulted in high blood levels (approximately 100 pg per milliliter). Blood-pressure response alone is not a good surrogate for survival; according to one report, a nitric oxide synthase inhibitor increased mean arterial pressure more than placebo did, yet significantly increased mortality from septic shock.<sup>4</sup> Thus, we cannot assume that a higher dose of vasopressin would be beneficial and safe.

When we set the sample size for VASST, we estimated that the mortality from septic shock would be 60%. However, the mortality in the control group in VASST was 39.3%, so the power was

less than originally planned. Landry and Oliver propose a three-group trial (norepinephrine alone, vasopressin alone, and the two combined), which raises two concerns. First, the sample-size requirements for three-group trials are onerous — much greater than those for two-group trials. Second, treating patients with vasopressin alone would be difficult because norepinephrine is used routinely as the standard of care.<sup>5</sup>

Mogyorosi asks about the rate of hyponatremia in VASST. Hyponatremia was recorded only if it was considered to be a serious adverse event, so the rate reported (0.3%) does not represent all cases of hyponatremia. Nonetheless, we found it reassuring that severe hyponatremia in the vasopressin group was extremely rare and was not more frequent than in the norepinephrine group. We did not use an algorithm for hyponatremia; fluid and electrolyte levels were managed by clinical teams at each center.

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## Five Genetic Variants Associated with Prostate Cancer

**TO THE EDITOR:** We agree with Zheng et al. (Feb. 28 issue)<sup>1</sup> that additional research is needed to assess the value of their finding of genetic variants associated with the risk of prostate cancer. Unfortunately, the planned marketing of a test based on this study<sup>2</sup> is premature and may cause more harm than good. Finding a genetic association is only the first step in the continuum of translating research into practice.<sup>3</sup> The results have not been independently confirmed, and adding the genetic test results to age, region, and family history only marginally improved risk prediction (the area under the curve [AUC] increased from 0.61 to 0.63). The clinical utility of the test is questionable because it cannot be used to reduce risk, since there are no known modifiable risk factors<sup>4</sup>; to encourage screening, since the balance of benefits and harms is unknown<sup>5</sup>; or to predict the clinical course of the disease, since the variants were associated equally with aggressive and nonaggressive cancers.<sup>1</sup> In the absence of evidence of improved outcomes, this test may lead to unnecessary or potentially harmful procedures.

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**TO THE EDITOR:** In his accompanying editorial, Gelmann states that the five polymorphisms reported by Zheng et al. do not yet constitute a viable screening test.<sup>1</sup> We think they never will. The use of genetic polymorphisms with modest odds