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## Vasopressin in septic shock: Clinical equipoise mandates a time for restraint\*

**V**asopressin use is rational in human septic shock. There is a vasopressin deficiency in septic shock, and vasopressin restores vascular tone in septic shock. Our group and others (1-12) showed that low-dose vasopressin (0.01-0.04 units/min) in vasodilatory shock decreases norepinephrine requirements, maintains blood pressure, and increases urine output. Thus, low-dose vasopressin could improve organ dysfunction and decrease mortality rate of septic shock.

In this issue, Dr. Klinzing and colleagues (13) evaluated vasopressin in septic shock by replacing norepinephrine with vasopressin to maintain blood pressure constant (mean vasopressin dose was 0.47 IU/min; range, 0.06-1.8 IU/min). Vasopressin decreased cardiac index, oxygen delivery, and oxygen uptake. Fractional splanchnic blood flow increased, yet the gastric  $P_{CO_2}$  gap increased. The authors conclude, and I agree, that "it would not appear beneficial to directly replace norepinephrine with vasopressin in septic shock." Dr. Klinzing and colleagues' study is important because it shows that simply replacing norepinephrine with vasopressin has deleterious consequences on global blood flow and complex effects on splanchnic perfusion. The dose of vasopressin was relatively high, making comparisons to low-dose vasopressin studies difficult. The unique strengths of Dr. Klinzing and colleagues' study include crossover from norepinephrine to vasopressin and measurement of splanchnic blood flow. Potential limitations are the small sample

size (n = 12), lack of randomization, and controversy regarding the indocyanine green determination of splanchnic blood flow and the gastric  $P_{CO_2}$  gap.

Persistent vasodilation and failure to increase mean arterial pressure and cardiac output in response to resuscitation characterize nonsurvivors of septic shock. Oxygen delivery must be maintained above a critical threshold, and arterial pressure must be adequate. Catecholamines are most often used. Recent studies favor norepinephrine (14), but norepinephrine has important adverse effects. Norepinephrine's  $\alpha$ -adrenergic effects decrease cardiac output, and norepinephrine at higher doses decreases renal blood flow and may decrease gut and myocardial perfusion. Norepinephrine increases pulmonary vascular resistance, and vascular responsiveness to norepinephrine diminishes.

Norepinephrine infusion results in nonphysiologic, high serum concentrations of norepinephrine. Yet mechanisms of cardiovascular dysfunction during sepsis are not directly related to catecholamines. For example, excessive activation of adenosine triphosphate-sensitive  $K^+$  channels (15), which close voltage-dependent  $Ca^{2+}$  channels, decreases calcium entry and leads to widespread dilation of arterial smooth muscle independent of catecholamines.

Vasopressin has little effect on arterial pressure normally. Vasopressin acts primarily as an antidiuretic hormone. During hypotension, vasopressin levels increase and maintain arterial blood pressure by vasoconstriction (16). Vasopressin is secreted by the posterior pituitary. Activation of  $V_1$  receptors on vascular smooth muscle causes vasoconstriction by blocking adenosine triphosphate-sensitive  $K^+$  channels (17). Activation of  $V_2$  receptors on renal tubules is respon-

sible for water resorption, vasopressin's antidiuretic effect. Activation of  $V_3$  pituitary receptors increases adrenocorticotropic hormone production (18). Vasopressin stimulates oxytocin receptors, which mediate vasodilation by stimulation of nitric oxide. Thus, there is organ-specific heterogeneity in the vascular responsiveness to vasopressin, and this vascular profile may be beneficial in septic shock. The study of Dr. Klinzing and colleagues (13) suggests potentially important differences between norepinephrine and vasopressin in gut blood flow distribution; however, the clinical impact is not clear in part because vasopressin increased gastric  $P_{CO_2}$  gap, which may indicate redistribution of blood flow away from the gut mucosa.

Patients with septic shock are sensitive to vasopressin (1, 4). Vasopressin stimulates  $V_1$ -mediated vasoconstriction and blocks adenosine triphosphate-sensitive  $K^+$  channels (17). Vasopressin potentiates effects of catecholamines. Vasopressin-induced vasoconstriction spares cerebral, coronary, pulmonary, and afferent glomerular capillary circulations (19, 20).

Human studies of vasopressin in vasodilatory shock are summarized in Table 1. There are studies in patients who had septic shock (1-5, 13), in postbypass patients (6-10), and in organ donors with vasodilatory shock (11). We reported a case series of 50 patients who received vasopressin for >2 hrs for septic shock (2). Vasopressin (average dose 0.05 IU/min) increased blood pressure significantly. Cardiac index decreased slightly. Vasopressin increased urine output by nearly 80%. Total vasopressor dose decreased by 33% at 4 hrs and by about 50% thereafter. However, hospital mortality rate was 85%. There were six cardiac arrests in patients receiving vasopressin.

\*See also p. 2646.

Key Words: human septic shock; vasopressin; norepinephrine; splanchnic blood flow; cardiac output  
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**Table 1.** Studies of low-dose vasopressin in human vasodilatory shock

Reference	Year	Study Type	No.	Patients	Endpoint Findings	Mortality Rate
Landry et al. (1)	1997	Case series	5	Septic shock	A, B, C	3/5
Landry et al. (4)	1997	Matched cohort	19	Septic shock	A, B, D in septic group	Not stated
			12	Cardiogenic shock		
Malay et al. (5) <sup>a</sup>	1999	RCT; placebo: N/S	10	Septic shock-trauma	A, B in treatment arm	0/5 in VP 2/5 in placebo
Argenziano et al. (7)	1998	Retrospective case series	40	Postbypass	A, B, D	
Argenziano et al. (6)	1997	RCT; placebo: N/S	10	Vasodilatory shock	A, B in treatment arm	Not stated
				Post-LVAD implantation	D in all	
Argenziano et al. (8)	1999	Case series	20	Vasodilatory shock; postcardiac transplant	A, B	
Rosenzweig et al. (9)	1999	Case series	11	Pediatric-vasodilatory shock postbypass	A, B, D	2/11: low CO
Morales et al. (10)	2000	Retrospective case series	50	Vasodilatory shock post-LVAD implantation	A, B	Not stated
Chen et al. (11)	1999	Case series	10	Organ donors with vasodilatory shock	A, D	Not stated
Holmes et al. (2)	2001	Retrospective case series	50	Septic shock	A, B, C	84% (42/50)
Patel et al. (3) <sup>a</sup>	2002	RCT:VP vs. NE	24	Septic shock	A, B, C, D	Not stated
Klinzing et al. (13)	2003	Crossover: NE to VP	12	Septic shock	B	Not stated
Gold et al. (12)	2000	Case series	7	Milrinone-hypotension	A, B, C	Not stated

A, increase in blood pressure; B, decrease or discontinuance of catecholamines; C, increase in urine output; D, low plasma vasopressin levels in patients; RCT, randomized, controlled trial; VP, vasopressin; N/S, normal saline; LVAD, left ventricular assist device; CO, cardiac output; NE, norepinephrine.

<sup>a</sup>Randomized, controlled trials in septic shock.

These patients were all in severe refractory septic shock.

Only three studies of vasopressin were randomized, controlled trials of vasopressin: ten trauma patients in septic shock (5), ten patients who had vasodilatory shock after implantation of a left ventricular assist device (6), and 24 patients who had septic shock (3). Total number of subjects was only 44! Vasopressin increased blood pressure and decreased catecholamine infusion dose requirements in these studies.

Only two studies (3, 13) compared norepinephrine to vasopressin in septic shock. Dr. Klinzing and colleagues (13) did a single crossover study from norepinephrine to vasopressin; Patel et al. (3) reported a pilot double-blind randomized controlled trial of vasopressin vs. norepinephrine. In Patel et al.'s small trial, study drug (either vasopressin or norepinephrine) was titrated to maintain mean arterial pressure, and open label vasopressors (including open label norepinephrine) were titrated down. There were no changes in cardiac index, mean arterial pressure, or systemic vascular resistance index with either norepinephrine or vasopressin. In the norepinephrine group, norepinephrine infusion rate changed from 24 to 28 µg/min. In the vasopressin group (dose 0.06 units/min), the open norepinephrine infusion decreased from 30 to 8 µg/min in 1 hr. Vasopressin doubled the urine output and increased

creatinine clearance. In contrast, norepinephrine did not change urine output or creatinine clearance. Vasopressin did not change gastric-arterial Pco<sub>2</sub> gradient.

The potentially beneficial effects of vasopressin in septic shock must be tempered with caution, because there are important examples of innovative treatments in critical care that had impressive results in early studies but in later studies were proved to increase mortality rate. Human growth hormone had strikingly positive effects on metabolic variables of critically ill adults. However, a randomized controlled trial showed that human growth hormone significantly increased mortality rate (21). Similarly, nitric oxide synthase inhibition by L-NG-methylarginine HCl increased mortality rate significantly in a multiple-center randomized controlled trial (22).

Because of these precedents, it is my impression that the vasopressin story is similar. There are beneficial short-term effects of vasopressin on hemodynamics and renal function in human septic shock; however, there are also potentially important adverse effects of vasopressin in human septic shock. Dr. Klinzing and colleagues' (13) study provides further insights into the limitations and adverse effects of vasopressin in septic shock. Thus, there is still true clinical equipoise regarding vasopressin in septic shock. I recommend restraint in clinical use of

vasopressin until it (like human growth hormone and nitric oxide synthase inhibition) has been tested in a randomized controlled trial powered for mortality rate.

James A. Russell, MD  
St. Paul's Hospital and the  
University of British  
Columbia  
McDonald Research Laboratories/  
The iCAPTURE Centre  
Vancouver, BC, Canada

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## Guidelines for critical care services and personnel—Innovations and improvements in patient care?\*

*Every system is perfectly designed to achieve the results it achieves.*

**G**uidelines, recommendations, clinical pathways, or pre-defined standards of care may well be suitable to optimize the process of care (1), decrease resource utilization (2), limit practice variation (3), and promote the implementation of evidence-based medicine in critical care practice (4). However, serious concerns have been raised about their effect on patient outcomes (5), physician autonomy (6), and malpractice risks (7).

In medicine, practice guidelines should represent “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances” (8). There is support from both

observational studies (9) and systematic reviews (10, 11) that, indeed, the process of guideline development will determine later acceptability by clinicians. In general, guidelines are more likely to be followed if they are evidence based (9) and were internally developed (10, 11). Controversial, vague, or nonspecific guidelines demanding extra resources, requiring new knowledge and skills, or provoking negative patient reactions are less likely to be adopted (9). Nevertheless, recommendations lacking formal evidence (i.e., solely based on expert opinion) may be of value as well (12) but need to be clearly specified and discussed as such.

The mindful reader of the “Guidelines on Critical Care Services and Personnel” (13) published in this issue of *Critical Care Medicine* has already noticed the considerable gap between the methodological requirements outlined previously and the recommendations presented by the Task Force of the American

College of Critical Care Medicine of the Society of Critical Care Medicine.

However, in contrast to previous recommendations for the delivery of health care in the intensive care unit (14–16), the authors took the level of evidence (from randomized, prospective, controlled investigations to published opinion) of all citations into account. Although the task force compiled an impressive number of recommendations relevant to various areas of intensive care unit organization, the vast majority remain based on expert opinion only (13).

More important, the disclosure of uncertainty present in the wording of some recommendation may provoke criticism: Despite the fact that adherence to vague and nonspecific recommendations remains questionable, rigid guidelines with inflexible instructions (e.g., “The following physician subspecialties should be available and able to provide bedside care within 30 mins,” or “The intensivist should be able to return more than 95%

\*See also p. 2677.

Key Words: guidelines; intensive care unit; process and organization; evidence-based medicine; methodology

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