THE USE OF VASOPRESSIN FOR SEPTIC SHOCK

SUMMARY
Vasopressin is an antidiuretic hormone that causes vasoconstriction in patients with septic shock. It has been shown to increase mean arterial pressure (MAP), systemic vascular resistance (SVR), and urine output and reduce or eliminate the need for catecholamines. Additionally, it may decrease cardiac output (CO). Although vasopressin use has been evaluated in a number of case reports and small studies, there is a lack of adequately powered, well-designed trials. The available literature primarily evaluates short-term hemodynamic effects. Potential disadvantages include coronary and splanchnic ischemia as well as a decrease in cardiac output. Consideration must also be given to the potentially detrimental effects of vasopressin-induced platelet aggregation in the setting of septic shock, a known procoagulant state. Finally, abrupt discontinuation may result in hypotension. Given the lack of well-designed trials and potential for serious adverse effects, the use of vasopressin for septic shock is not recommended at this time.

INTRODUCTION
Vasopressin is an antidiuretic hormone that is produced in the hypothalamus and stored in the pituitary. It is released in response to elevated serum osmolality, hypovolemia, and hypotension. In normal, well-hydrated patients, serum concentrations are < 4 pg/mL (1). However, in the setting of vasodilatory or septic shock, there is an early transient increase followed by a decline to inappropriately low levels. This may result from depletion of neurohypophyseal stores following excessive stimulation or it may result from inhibition of release (1).

Vasopressin has little pressor effect in normal subjects. However, in the setting of shock, vasopressin stimulates V1 receptors located on vascular smooth muscle and leads to vasoconstriction. It also potentiates the effects of catecholamines. It can cause vasodilation of some vascular beds, which is likely mediated by nitric oxide release (1).

The possibility of using a low-dose infusion as an adjunctive or alternative vasopressor in patients who become refractory to catecholamines is appealing. However, consideration must be given to the well-known adverse ischemic events associated with this agent. Additional effects, such as stimulation of platelet aggregation via release of factor VIIIc and von Willebrand factor must also be considered.

LITERATURE REVIEW
Landry and colleagues evaluated whether or not vasopressin deficiency contributes to vasodilation in patients with septic shock (2). Nineteen patients refractory to fluid administration and catecholamine infusion for 1-2 days were included. Those with a diagnosis of active coronary artery disease or mesenteric ischemia were excluded. Patients with cardiogenic shock were included for comparison. Vasopressin serum concentrations were found to be significantly lower in patients with septic shock as compared to those with cardiogenic shock (3.1 pg/mL versus 22.7 pg/mL, respectively). Ten patients received vasopressin via a central line at 0.04 units/minute. Catecholamines were weaned for a systolic
blood pressure $> 130$ mmHg. Compared to baseline values, vaspressin infusion resulted in a significant increase in both blood pressure and SVR, with a significant decrease in CO. These changes occurred within 15 minutes. No significant change in heart rate was found. Six of the 10 patients were weaned off catecholamines within 15 minutes and were maintained on vasopressin alone at 0.01 units/minute. (Class II)

Malay and colleagues conducted a randomized, double-blind, placebo-controlled trial evaluating the hemodynamic effects of low-dose vasopressin in 10 patients with septic shock (3). All had a cardiac index (CI) $> 2.5$ L/minute and a MAP $< 70$ mmHg, despite the use of catecholamines (dopamine $> 3$ mcg/kg/minute and any dose of norepinephrine and/or phenylephrine). Patients were randomized to placebo or vasopressin (administered via a central line at 0.04 units/minute). Weaning of catecholamines for a MAP $> 70$ mmHg began 1 hour following initiation of the study drug. Patients were critically ill as evidenced by a mean APACHE II score of 27 and 26 in the treatment and placebo groups respectively. Baseline hemodynamic data revealed a significantly higher CI in the placebo group. Vasopressin administration resulted in significant increases in systolic blood pressure (SBP), MAP, and SVR within 1 hour. No significant difference in heart rate or CI was found. At 24 hours, all vasopressin patients were weaned from catecholamines (except for dopamine at 3 mcg/kg/min) compared to none of the remaining placebo patients. (Class I)

Holmes and colleagues performed a retrospective study evaluating the hemodynamic and renal effects of vasopressin in 45 patients with septic shock (4). Patients receiving vasopressin for at least 2 hours were included. Patients were severely ill with an average baseline APACHE II score of 27. Vasopressin doses were variable, ranging from 0.01 – 0.6 units/minute, with an average of 0.05 units/minute during the 48 hour evaluation period. There was a significant increase in MAP at all evaluation points (4, 24, and 48 hours) and a significant decrease in CI at 4 hours. Urine output was significantly increased at 4 hours. A significant decrease in the mean catecholamine use was found at all evaluation points. No significant change in systolic pulmonary artery pressure was noted. Doses beyond 0.04 units/minute did not result in further hemodynamic improvements. Six patients experienced cardiac arrest during vasopressin infusion. Four were receiving doses $>0.05$ units/minute. (Class III)

Tsuneyoshi and colleagues performed a prospective study to determine the cardiovascular and metabolic effects of low-dose vasopressin (5). Sixteen patients with septic shock and persistent hypotension (SBP $< 80$ mmHg or MAP $< 60$ mmHg) despite adequate fluid resuscitation and catecholamine infusion (norepinephrine $\geq 0.2$ mcg/kg/min) were enrolled. Patients with hypovolemia, coronary artery disease, or heart failure were excluded. Vasopressin was administered through a central venous catheter at 0.04 units/minute for 16 hours. Vasopressin infusion resulted in significant increases SBP, MAP, and SVR within two hours. These effects persisted throughout the 16-hour study period. Significant improvements in urine output also occurred. There were no significant changes in heart rate or CI. Fourteen of 16 patients stabilized and did not require additional fluid or catecholamine therapy. Attempts to discontinue vaspressin resulted in hypotension necessitating continued administration (range of 18-284 hours). Vasopressin serum concentrations increased from a mean of 7.3 pg/ml at baseline to 289.3 pg/mL during the vasopressin infusion. No episodes of myocardial, skin, or intestinal ischemia were detected. (Class II)

Patel and colleagues performed a prospective, randomized, double-blind study comparing vasopressin and norepinephrine for 4 hours in 24 patients with severe septic shock that required high-dose vasopressors despite fluid resuscitation (6). Patients with acute coronary artery disease, mesenteric ischemia, severe hyponatremia, or Raynaud’s phenomenon were excluded. Vasopressin and norepinephrine were started at 0.01 units/minute and 2 mcg/minute, respectively. The maximum doses allowed were 0.08 units/minute of vasopressin and 16 mcg/minute of norepinephrine. Norepinephrine was decreased from 20 to 17 mcg/minute in the norepinephrine group and from 25 to 5.3 mcg/minute in the vasopressin group. The median vasopressin dose was 0.06 units/minute. (Class I)

In addition to the above studies, a number of case reports evaluate the use of vasopressin (7-10).
REFERENCES