Vasopressin in the ICU
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Purpose of the review
Vasopressin is one of the most important endogenously released stress hormones during shock. In this review, studies published in the past year that add to our understanding of the use of vasopressin in the ICU are discussed.

Recent findings
Endogenous vasopressin levels are inappropriately low in adults with severe sepsis but not in children with meningococcal septic shock. Vasopressin but not norepinephrine improved renal blood flow and oxygen delivery and prolonged survival in animal models of septic shock. In human vasodilatory shock, the combination of low-dose vasopressin and norepinephrine was found to be safe and effective. In humans, vasopressin can cause gastrointestinal hypoperfusion and ischemic skin lesions. In hypodynamic animal models of sepsis vasopressin compromised oxygen delivery and decreased systemic and gut blood flow.

High-dose bolus vasopressin appeared promising in animal studies of hemorrhagic shock and cardiopulmonary arrest and in a large, randomized clinical trial of vasopressin versus epinephrine in human cardiopulmonary arrest with asystole. However, poor neurologic outcomes raised controversy in introducing vasopressin into CPR guidelines.

Summary
There is growing evidence that vasopressin infusion in septic shock is safe and effective. Several studies published this year support the hypothesis that vasopressin should be used as a continuous low-dose infusion (between 0.01 and 0.04 U/min in adults) and not titrated as a single vasopressor agent. However, multiple studies highlight the clinical equipoise that exists regarding the use of vasopressin in vasodilatory shock. Guidelines on management of septic shock recommend “cautious use of vasopressin pending further studies.”

Keywords
vasopressins, sepsis syndrome, septic shock, CPR, hemorrhagic shock

Introduction
Vasopressin is one of the most important endogenously released stress hormones, especially during shock. The rationale for use of vasopressin in the ICU is that there is a vasopressin deficiency in vasodilatory shock and advanced shock from any cause and that exogenously administered vasopressin can restore vascular tone. Vasopressin restores vascular tone in vasoplegic (catecholamine-resistant) shock states by at least four known mechanisms: through activation of V1Rs, modulation of K$_{ATP}$ channels, modulation of nitric oxide, and potentiation of adrenergic and other vasoconstrictor agents [1]. Paradoxically, vasopressin has also been demonstrated to cause vasodilation in some vascular beds, distinguishing this hormone from other vasoconstrictor agents. In a recent review, the seemingly paradoxical vasodilatory and vasoconstrictor actions of vasopressin were explained by a discussion of the signaling pathways and distribution of vasopressin receptors [2••]. In a second review, the mechanisms of vasoconstriction and vasodilation of the vascular smooth muscle were discussed, with emphasis on vasopressin interaction in these pathways [3••].

The goal of this review is to highlight studies that have been published in the past year that add to our understanding of the use of vasopressin in shock states in the ICU.

Vasopressin in vasodilatory shock states

Endogenous vasopressin levels
Two studies examined endogenous vasopressin levels in human septic shock. Established septic shock in adults is associated with a vasopressin deficiency
Vasopressin levels were determined in 62 consecutive septic shock patients in this study [4]. Vasopressin deficiency was defined as by a plasma vasopressin level of ≤ 3.6 pg/mL, associated with hyponatremia or a systolic blood pressure of < 100 mm Hg at the time of blood sampling. Relative vasopressin deficiency was seen in approximately one third of patients with late septic shock. In the early phase of septic shock, vasopressin levels were increased, although at a much lower level (4.3–21 pg/mL) than previous reports. Vasopressin levels decreased significantly from baseline to hour 96 after shock onset, and most patients exhibited relative vasopressin deficiency by 36 hours from shock onset.
Meningococcal septic shock in children is not associated with a vasopressin deficiency
Data regarding vasopressin levels in children with septic shock are scarce except for reports of vasopressin depletion in three children with vasodilatory shock after cardiac surgery [5] and 11 children with septic shock [6]. In this study, admission vasopressin levels were studied in children with meningococcal septic shock [7]. Eighteen of 19 children with meningococcal septic shock (seven deaths) and 15 children with meningococcal infection without shock (no deaths) were included. In children with meningococcal septic shock, median admission vasopressin level was 41.6 pg/mL (range, 1.4–498.9) and in those without shock, it was 3.3 pg/mL (range, 1.6–63.8). In children with meningococcal septic shock, the vasopressin level was not correlated with duration of shock (range, 1–8 hours). Vasopressin levels were higher in nonsurvivors but not significantly so. Only one patient who did not survive had an admission vasopressin level < 30 pg/mL. This study suggests that vasopressin administration may not be as beneficial in children with meningococccemia compared with adults with septic shock-induced vasopressin deficiency, although the authors encourage further studies including serial vasopressin level assessments in children.

Vasopressin infusion and outcome in vasodilatory shock
There were two human outcome studies and one animal survival study.

Catecholamine-resistant septic shock is responsive to a combined infusion of low-dose vasopressin and norepinephrine
Forty-eight patients with catecholamine-resistant vasodilatory shock owing to cardiopulmonary bypass with or without sepsis were randomized to low-dose vasopressin infusion combined with norepinephrine or norepinephrine alone [8••]. More patients in the norepinephrine alone group developed tachyarrhythmias. There were no differences in the incidence of myocardial ischemia and myocardial infarction between groups. Gastrointestinal perfusion (assessed by gastric tonometry) was better preserved in the vasopressin and norepinephrine group. The authors conclude that the combined infusion of low-dose vasopressin and norepinephrine proved to be superior to infusion of norepinephrine alone in the treatment of cardiocirculatory failure in catecholamine-resistant vasodilatory shock.

Prophylactic vasopressin administration was of benefit in patients at risk of vasodilatory shock related to cardiopulmonary bypass
In this double-blind, randomized trial, cardiac surgical patients on angiotensin-converting enzyme inhibitor therapy were randomized to receive vasopressin (0.03 U/min) (n = 13) or an equal volume of normal saline (n = 14) starting 20 minutes before cardiopulmonary bypass [9••]. Vasopressin did not change pre–cardiopulmonary bypass mean arterial pressure or pulmonary artery pressure. After cardiopulmonary bypass, the vasopressin group had a lower peak norepinephrine dose than the placebo group, a shorter period on catecholamines, fewer hypotensive episodes, and a shorter ICU length of stay (1.2 ± 0.4 vs 2.1 ± 1.4 days, P = 0.03). Two patients initially randomized to receive placebo could not be weaned from cardiopulmonary bypass because of intractable vasodilatory shock on norepinephrine and were administered open-label vasopressin with success. No episodes of intractable vasodilatory shock were observed in the vasopressin group. Two complications occurred in each group: acute renal insufficiency and right heart failure in the vasopressin group and acute renal insufficiency and lethal hemorrhage in the normal saline group. No instances of postoperative myocardial infarction, hepatic insufficiency, intestinal infarction, limb digit ischemia, or stroke were noted in either group. In this study, prophylactic administration of vasopressin, at a dose without a vasoressor effect before cardiopulmonary bypass, reduced post–cardiopulmonary bypass hypotension and vasoconstrictor requirements and was associated with a shorter ICU stay [9••].

Vasopressin infusion administered to sheep with septic shock prolonged survival
In this survival study in animals, peritonitis was induced by 1-cm cecal perforation. Vasopressin (0.02 U/min) was compared with norepinephrine alone or the combination of low-dose vasopressin (0.01 U/min) and norepinephrine or norepinephrine alone versus control animals (no vasopressor administered) after hypotension ensued [10•••]. The survival time was significantly longer in all treatment groups than in the control group and was longer in the vasopressin and vasopressin plus norepinephrine groups than in the norepinephrine alone group. Cardiac output increased in all groups after the induction of peritonitis, consistent with a hyperdynamic model of sepsis. Cardiac output was significantly lower in the vasopressin group than in the vasopressin plus norepinephrine group. Superior mesenteric arterial blood flow was significantly lower in the vasopressin plus norepinephrine group than in the vasopressin group. Gastric perfusion (measured by gastric tonometry) was better preserved in the vasopressin plus norepinephrine group compared with all other groups. Urine output was higher in the vasopressin group than in the control and norepinephrine groups. On necropsy, small intestine edema and congestion were less severe and kidneys showed less severe congestive damage in the vasopressin plus norepinephrine group. In summary, in this clinically relevant model of septic shock caused by peritonitis, low-dose vasopressin administration (alone or with norepinephrine) prolonged survival.
Vasopressin infusion improves renal blood flow
There were two animal studies examining the differential effects of vasopressin and norepinephrine on the renal circulation.

Vasopressin but not norepinephrine improved renal blood flow and oxygen delivery in animal models of septic shock
An animal study was conducted to assess systemic, splanchnic, and renal hemodynamics and metabolic effects of vasopressin infusion compared with norepinephrine during resuscitation from endotoxemia [11]. Animals were randomized to receive norepinephrine 0.2 µg/kg/min or vasopressin infusions at relatively high doses (0.08 U/min in 20-kg mongrel dogs) after induction of endotoxemia by lipopolysaccharide infusion and fluid resuscitation. Vasopressin infusion restored renal blood flow and DO2 in endotoxemia compared with animals resuscitated with norepinephrine, which had persistently low renal blood flow and DO2 (Fig. 1). The authors speculate that the observed improvement in renal blood flow was likely secondary to nitric oxide–mediated afferent arteriolar vasodilatation and selective efferent arteriolar vasoconstriction [11].

A second endotoxemia animal study examined the short-term effects of vasopressin (0.02 U/kg/h) compared with norepinephrine (2 µg/kg/min) [12]. Despite identical effects on mean arterial pressure, cardiac output, and renal blood flow, vasopressin and norepinephrine exhibited differential effects on diuresis and renal function. Vasopressin but not norepinephrine attenuated the declines in diuresis and inulin clearance induced by endotoxemia. The authors concluded that vasopressin improves systemic hemodynamics without side effects and has particular beneficial effects on renal function [12].

Vasopressin and the splanchnic circulation
Vasopressin worsened gastrointestinal perfusion in two human studies and one animal study.

In norepinephrine-dependent patients in septic shock, continuous infusion of low-dose vasopressin results in gastrointestinal hypoperfusion
In an observational study of 13 patients in established septic shock requiring norepinephrine to maintain blood pressure [13], vasopressin infusion at 0.04 U/min resulted in an increase in mean arterial pressure without a decrease in cardiac index. Plasma vasopressin levels increased from 17 to 230 pg/mL after 4 hours of infusion. The difference between gastric and arterial CO2 partial pressure (P(g-a)CO2 gap) increased from 5 mm Hg at baseline to 19 mm Hg on vasopressin infusion. Interestingly, there was a strong correlation between median plasma levels of vasopressin and the median P(g-a)CO2 gap ($r^2 = 0.98$).

High-dose vasopressin infusion in patients with septic shock redistributed gut blood flow to the disadvantage of the mucosa
In 13 patients with septic shock, high doses of vasopressin (mean dose, 0.47 U/min) were used to replace norepinephrine (mean dose, 0.56 µg/kg/min) [14••]. Vasopressin infusion caused significant changes in global hemodynamics with a decrease in heart rate and cardiac index. Global oxygen delivery decreased significantly.
Hepatosplanchnic blood flow (measured by continuous infusion of indocyanine green) tended to increase, whereas gastric regional PCO₂ gap increased significantly, suggesting that the gut blood flow could have been redistributed to the disadvantage of the mucosa. Based on these limited data, it does not appear beneficial to directly replace norepinephrine with vasopressin in septic shock [14••].

Vasopressin infusion in an animal model of septic shock worsened systemic and gut flow
In a porcine model of endotoxic shock, the effects of high-dose vasopressin (0.04 U/min in 30-kg animals) on regional blood flow were studied using ultrasonic transit time flow probes [15]. In this hypodynamic model of sepsis (endotoxin infusion was associated with decreased cardiac output), vasopressin reversed hypotension but decreased systemic and gut blood flow. This was associated with hyperlactatemia, signs of visceral dysoxia, and jejunal luminal lactate release. In contrast, norepinephrine did not compromise either systemic or regional blood flow or tissue oxygenation. The authors conclude that these results may be owing to an excessive dose of vasopressin and reasonably speculate that combining low-dose vasopressin with inotropes might have counteracted the side effects of vasopressin seen in this model.

Vasopressin infusion and ischemic skin lesions
In a retrospective analysis of 64 critically ill patients with catecholamine-resistant vasodilatory shock, vasopressin infusion (dose range, 0.067–0.1 U/min) was associated with ischemic skin lesions in 19 of 63 patients (30%) [16•]. Most of the skin lesions occurred on the distal limbs (68%), 21% occurred on the distal limbs and trunk, and 26% occurred on the tongue. Neither amputation of limbs nor plastic surgical interventions were performed in any of the patients. Multiple logistic regression analysis revealed that presence of septic shock and preexistent peripheral arterial occlusive disease were significant independent risk factors for the development of ischemic skin lesions during vasopressin infusion.

Vasopressin and cardiac output
During ovine endotoxia, infusion of vasopressin titrated to mean arterial pressure (mean dose, 0.04 U/min) decreased cardiac index, compromised oxygen delivery, and increased pulmonary vascular resistance index [17•]. When norepinephrine was infused along with vasopressin, the decrease in cardiac index was ameliorated. The authors conclude that although vasopressin infusion alone (titrated to mean arterial pressure) caused detrimental effects on oxygen delivery, a simultaneous infusion of vasopressin and norepinephrine may represent a superior therapeutic option [17•].

Dose of vasopressin in vasodilatory shock
In general, vasopressin infusions have been administered in two ways. One approach has been to titrate vasopressin to mean arterial pressure, just as conventional vaso-

pressor agents are used. A second approach is to use a continuous low-dose infusion of vasopressin (between 0.01 and 0.03 U/min in adults) that restores “physiologic” concentrations of vasopressin in the plasma [18].

In a porcine model of endotoxic shock, the effect of increasing doses of vasopressin was studied [19••]. In this study, pigs were administered vasopressin or phenylephrine in incremental doses after shock was induced by endotoxin administration and ultrasonic flow probes measured microcirculatory flow. Low doses of vasopressin (typically used in the clinical management of septic shock) increased arterial pressure by increasing systemic vascular resistance without a significant preferential effect on the circulations measured. However, moderately higher doses of vasopressin induced ischemia in the mesenteric and renal circulations. The authors concluded that the data indicate that the safe dose range for exogenous vasopressin in septic shock is narrow and support the current practice of fixed low-dose administration, generally <0.04 U/min and in no case exceeding 0.1 U/min [19••].

Other investigators support the concept that vasopressin should not be used as a single vasopressor agent in septic shock and that if vasopressin is used in advanced vasodilatory shock outside of clinical trials, it should be considered only as a supplementary vasopressor to avoid detrimental reductions of cardiac output, global oxygen delivery, and gut mucosal blood flow [20].

Vasopressin in cardiopulmonary arrest
Several animal studies and one large human randomized, controlled trial examined the effect of high-dose bolus vasopressin in cardiopulmonary arrest.

Animal studies of cardiopulmonary arrest
In a study to designed to evaluate the effects of a combination of vasopressin and epinephrine during prolonged CPR on neurologic outcome in pigs, vasopressin/epinephrine administration, but not epinephrine or saline placebo alone, ensured long-term survival with full neurologic recovery [21].

In a porcine model of cardiopulmonary arrest, vasopressin and epinephrine resulted in comparable mean arterial blood pressure and adrenal gland cortex blood flow [22]. Vasopressin, however, produced significantly higher adrenal medullary blood flow during the entire experiment when compared with both the epinephrine and placebo groups. Seven of seven vasopressin animals but only one of six epinephrine animals and none of six placebo pigs were successfully defibrillated.

In a study to investigate the influence of vasopressin and amiodarone on CPR outcome in a pig model of hypothermic cardiac arrest, vasopressin significantly increased
coronary perfusion pressure and defibrillation success [23]. Owing to refibrillation within 30 to 150 seconds, the 60-minute survival rate was not improved by vasopressin. Subsequent drug therapy with amiodarone had no further effect on defibrillation success or the refibrillation rate.

**Human cardiopulmonary arrest**

In a randomized, controlled trial, 1219 adults who had had an out-of-hospital cardiac arrest were randomly assigned to receive two injections of either 40 U vasopressin or 1 mg epinephrine, followed by additional treatment with epinephrine if needed [24]. The primary end point was survival to hospital admission, and the secondary end point was survival to hospital discharge. There were no significant differences in the rates of hospital admission between the vasopressin group and the epinephrine group either among patients with ventricular fibrillation (46.2% vs 43.0%, \( P = 0.48 \)) or among those with pulseless electrical activity (33.7% vs 30.5%, \( P = 0.65 \)). Among patients with asystole, however, vasopressin use was associated with significantly higher rates of hospital admission (29.0% vs 20.3% in the epinephrine group, \( P = 0.02 \)) and hospital discharge (4.7% vs 1.5%, \( P = 0.04 \)). Among 732 patients in whom spontaneous circulation was not restored with the two injections of the study drug, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group but not in the epinephrine group (hospital admission rate). The authors concluded that the effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity, but vasopressin was superior to epinephrine in patients with asystole and that vasopressin followed by epinephrine may be more effective than epinephrine alone in the treatment of refractory cardiac arrest. An accompanying editorial urged practitioners to incorporate the use of vasopressin into their resuscitation protocols immediately [25].

The conclusions of this study and the accompanying editorial have been criticized by those who cite the lack of a significant difference between groups in the rates of survival to hospital admission and survival to hospital discharge overall [26] and a very small difference in the asystole group (CIs include unity) [27]. Additionally, more than 50% of long-term survivors in the overall vasopressin group had a neurologic outcome described as severe cerebral disability or worse [28].

In summary, vasopressin is a possible alternative to epinephrine in patients with asystole and particularly in patients who do not have a response to initial treatment with epinephrine. However, providers are urged to wait for and to participate in the international evidence-evaluation process before changing resuscitation protocols [26].

**Vasopressin in hemorrhagic shock**

The goals of therapy in hemorrhagic shock are to restore oxygen perfusion to the tissues and to stop hemorrhage, usually through operative intervention. Although rapid transport of the patient to definitive care is universally agreed on, controversy exists as to the timing and delivery of fluid therapy in traumatic hemorrhage [29]. Animal studies strongly suggest that limited or hypotensive resuscitation may be preferable for the trauma victim with the potential for ongoing uncontrolled hemorrhage, termed limited resuscitation. There have been three recent studies of vasopressin in uncontrolled hemorrhagic shock.

Vasopressin was compared with fluid resuscitation and to no resuscitation in a porcine model of hemorrhagic shock [30]. Twenty-three animals were randomly assigned to receive at the point of experimental intervention (mean arterial pressure < 20 mm Hg) either 0.4 U/kg vasopressin followed by an infusion of 0.08 U/kg/min or an equal amount of saline placebo or fluid resuscitation (25 mL/kg of Ringer and 25 mL/kg of 3% gelatin solution). After 30 minutes of experimental therapy, bleeding was controlled by surgical intervention in all hemodynamically stable pigs. Maximal mean arterial blood pressure during experimental therapy was significantly higher in the vasopressin group than in the placebo or fluid resuscitation groups. Pigs treated with vasopressin had relatively stable hemodynamic variables, whereas seven of seven fluid resuscitation and seven of seven saline placebo animals deteriorated, and all resulted in pulseless electrical activity before surgical intervention was initiated. Nine of nine vasopressin pigs were drinking and eating 24 hours after successful resuscitation and had normal levels of consciousness and behavior. Vasopressin, but not fluid resuscitation or saline placebo, ensured survival with full recovery in this liver trauma model with uncontrolled and otherwise lethal hemorrhagic shock in pigs.

These findings were duplicated in a study with almost identical design [31]. Seven of seven vasopressin pigs survived until bleeding was surgically controlled compared with none in the saline placebo or fluid resuscitation groups. The authors speculate that vasopressin may reflect two advantages in uncontrolled hemorrhagic shock in the abdomen: It may decrease bleeding first by shifting blood away from the injury and by improving vital organ blood flow. In summary, vasopressin, but not saline placebo or fluid resuscitation, significantly improves short-term survival during uncontrolled hemorrhagic shock.

In a similar animal study of uncontrolled liver hemorrhage, 23 pigs were randomly assigned to receive 0.4
U/kg/min vasopressin followed by a vasopressin infusion, 45 μg/kg epinephrine followed by an epinephrine infusion, or saline placebo in an equal volume after hypotension ensued [32•]. Vasopressin but not epinephrine or saline placebo resulted in a significant increase in mean arterial pressure. Arterial blood pressure and heart rate deteriorated in the epinephrine group, despite a second bolus of epinephrine, and in the saline placebo groups, and by 15 minutes, all animals died. In contrast, none of the vasopressin animals required a second bolus of vasopressin and all animals survived to surgery. Most strikingly, administration of vasopressin was accompanied by immediate hemostasis of the venous bleeding from the liver. Interestingly, despite an ongoing vasopressin infusion, blood flow to the gut returned to 25% of baseline levels within 10 minutes after drug administration. In summary, vasopressin, but not epinephrine or saline placebo, improved short-term survival in a porcine model of uncontrolled hemorrhagic shock after liver injury when surgical intervention and fluid replacement were delayed.

**Conclusion**

In conclusion, there has been a profusion of studies in the past year that contribute to our understanding of the use of vasopressin in the ICU. In several small human studies and one animal survival study, the infusion of low-dose vasopressin (“physiologic” replacement dose ≈ 0.04 U/min) appears to be safe and effective. Most studies examining the effects of vasopressin on renal blood flow are encouraging. Some of the animal studies and one human study supported the experimental effect of vasopressin on the splanchnic circulation; however, two caveats exist. Many animal studies use a hypodynamic (low cardiac output) model of sepsis that does not mimic human septic shock. Second, the dose of vasopressin seems to be very important; investigators caution that the dose of vasopressin should not exceed 0.04 U/min [18], and others conclude that vasopressin should not be used as a single vasopressor agent in septic shock [14••,20].

The use of high-dose bolus vasopressin appears to be of benefit in several animal models of cardiopulmonary arrest and uncontrolled hemorrhagic shock. A large multicenter study of vasopressin versus epinephrine reported a survival advantage (but poor neurologic outcome) in asystolic cardiopulmonary arrest. Controversy still exists regarding the implementation of vasopressin in cardiopulmonary arrest protocols.

Finally, despite an increasing literature on the use of vasopressin in the ICU, a recent document of guidelines to improve outcome in severe sepsis and septic shock concluded that although low doses of vasopressin may be effective in increasing blood pressure in patients refractory to other vasopressors, no outcome data are available and recommended “cautious use of vasopressin pending further studies” [33••]. We agree with others that if vasopressin is used in advanced vasodilatory shock outside of clinical trials, it should be considered only as a supplementary vasopressor and in doses not exceeding 0.04 U/min.

**References and recommended reading**

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- Of outstanding interest

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