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SPECIAL FEATURE

Vasopressin Use in Septic Shock

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Dr. Hammond reports no financial relationships relevant to this field of study.

Septic shock is associated with significant costs and sequelae, as well as mortality rates of 20-50%.[1] Current management of septic shock includes early administration of intravenous fluids, antimicrobial agents, and vasopressor support. While norepinephrine is recommended as the first-line vasopressor for septic shock in the 2016 Surviving Sepsis Campaign guidelines, vasopressin is a second-line vasopressor option that may be added to norepinephrine to reduce catecholamine requirements and achieve a target mean arterial pressure (MAP).[2,3]

Patients with catecholamine-refractory septic shock often are sensitive to exogenous vasopressin administration.[4] Plasma vasopressin concentrations initially increase in response to relative hypotension and decreased vascular resistance but decline within six to 36 hours to sub-physiological concentrations because endogenous vasopressin stores have been depleted. The synthesis and release of vasopressin may be impaired for up to seven days after septic shock onset.[5] Despite the potential benefits to resolving this relative vasopressin-deficient state, many controversies still exist regarding vasopressin use in septic shock.

TIMING OF VASOPRESSIN INITIATION

The timing of vasopressin initiation may play a crucial role in septic shock management. The Vasopressin in Septic Shock Trial (VASST) found that administering vasopressin within 12 hours following norepinephrine initiation compared to remaining on norepinephrine monotherapy had a similar rate of 28-day mortality in the full trial cohort (35.4% vs. 39.3%; $P = 0.26$). However, in a subgroup of patients with less severe septic shock (norepinephrine infusion rate ≤ 14 mcg/min), patients in the vasopressin group had a lower mortality at 28 days (27% vs. 36%; $P = 0.05$).[5] Because this benefit was found in a subgroup analysis of VASST, and vasopressin initiation could

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have been provided earlier in clinical care, additional studies have investigated the effects of earlier vs. later vasopressin addition to catecholamine vasopressors.[6-9]

In a retrospective, single-center study (n = 72), researchers investigated the effects of vasopressin that was administered earlier (within six hours of catecholamine vasopressor initiation) vs. later (between six and 48 hours of catecholamine vasopressor initiation).[6] Shock duration and catecholamine vasopressor requirements were similar between groups, although patients receiving earlier initiation of vasopressin experienced a new-onset arrhythmia less frequently (37% vs. 64%; *P* = 0.001). In another retrospective study (n = 96), researchers observed that earlier vasopressin initiation (within four hours of septic shock recognition) was associated with reduced time to achieve and maintain a MAP of 65 mmHg for at least four hours (six vs. 10 hours; *P* = 0.02) and greater reductions in Sequential Organ Failure Assessment (SOFA) scores at 72 hours (-4 vs. -1; *P* = 0.01).[7] The incidence of new-onset arrhythmia was similar between groups, although only arrhythmias requiring clinical intervention were compared. The reduced time to achieve and maintain target MAP was confirmed in a trial at the same institution.[8] Conversely, in a pre-post study that evaluated the effects of a restriction on vasopressin use to patients receiving greater than 50 mcg/min of norepinephrine as opposed to greater than 10 mcg/min of norepinephrine, researchers did not observe a difference in time to achieve a MAP of 65 mmHg for one hour, new-onset arrhythmia, or ICU and hospital mortality rates.[9] Finally, the Vasopressin vs. Norepinephrine as Initial therapy in Septic Shock (VANISH) trial also showed no mortality benefit from earlier vasopressin therapy (within six hours of shock recognition), although the primary outcome was focused on kidney failure-free days within a 28-day period after randomization.[10] Most patients in the vasopressin group were receiving concomitant norepinephrine.

Although earlier use of vasopressin does not appear to confer a mortality benefit compared to later use, the optimal time to initiate vasopressin remains unknown. This is especially relevant in the era of personalized medicine. Plasma vasopressin levels could guide vasopressin therapy by targeting physiologic levels while avoiding higher concentrations that could lead to adverse effects. However, measurement of plasma vasopressin levels is challenging because vasopressin has a short half-life, is unstable ex-vivo, and requires a cumbersome analytical process for measurement.[11] Although copeptin, the C-terminal of a vasopressin precursor, is stable in plasma, easier to measure than vasopressin, and correlates well with vasopressin plasma concentration, its use may be inadequate in select clinical scenarios, such as in patients receiving veno-venous hemofiltration.[12,13] The clinical utility of measuring vasopressin or copeptin levels in septic shock requires further investigation.[14]

RANGE FOR VASOPRESSIN DOSING

The optimal vasopressin dosage that facilitates adequate hemodynamic response while limiting adverse effects remains controversial. The 2016 Surviving Sepsis Campaign guidelines recommend a maximum vasopressin rate of 0.03 units/minute because higher rates may increase the risk of limb, digital, and mesenteric ischemia.[3,15] Ischemic skin lesions with vasopressin have been reported with doses approaching 0.06 to 0.09 units/min in 70-100 kg patients.[16] A prospective, randomized, controlled trial compared lower (0.033 units/minute) and higher (0.067 units/minute) vasopressin dosages (n = 50) in septic shock requiring norepinephrine rates greater than 0.6 mcg/kg/minute.[17] Patients in the higher-dose vasopressin group had lower norepinephrine requirements at 48 hours (0.22 ± 0.16 vs. 0.4 ± 0.31 mcg/kg/minute, *P* = 0.006). Vasopressin serum concentrations were higher in the high-dose group, but were elevated in both groups. Despite this, adverse events were similar between groups, although digital ischemia was not evaluated.[17] Patients who received vasopressin in the VANISH trial were exposed to 0.01 to 0.06 units/minute of vasopressin, which was up to twice the rate used in VASST.[5,10] The VANISH trial did not detect a mortality benefit from the higher vasopressin dosage and reported a

numerically greater incidence of digital ischemia in the vasopressin group (5% vs. 1.5%, 97.5% confidence interval [CI], for risk difference -0.1 to 7.9).

As a general practice, lower-dose vasopressin (e.g., 0.03 units/minute) should be initiated in septic shock and may be titrated to the lowest dosage at which an adequate hemodynamic response is observed.[5,18-21] Vasopressin has an apparent half-life of less than 10 minutes, which necessitates a slower titration strategy (i.e., every 30-50 minutes) than catecholamine vasopressors that have half-lives of less than two minutes. The optimal target plasma vasopressin concentration in septic shock remains controversial, with physiologic and supraphysiologic targets being considered at this time.[22,23] Vasopressin provided as a continuous infusion at 0.03 units/minute has been proposed to achieve adequate serum vasopressin concentrations and decrease catecholamine vasopressor requirements without an increase in adverse events.[5] Finally, vasopressin dosages up to 0.06 units/minute should be reserved for consideration in patients with septic shock refractory to conventional vasopressor dosing.[10] Close monitoring for adverse events, particularly reduced liver function, bradycardia, and digital ischemia, should be performed.

FIXED VS. WEIGHT-BASED VASOPRESSIN DOSING

Catecholamine vasopressors are titrated to a specific MAP goal and commonly are dosed based on a patient's body weight. In contrast, vasopressin is conventionally administered as a fixed, non-weight-based dose continuous infusion. Dosing that is provided irrespective of body weight may predispose patients at each end of the weight spectrum to disparate vasopressin exposure, which may increase the odds for toxicity or decrease the odds for efficacy. Several retrospective evaluations have investigated the interaction between fixed-dose vasopressin and body weight.[24-28]

In a retrospective analysis of VASST comparing patients based on their body mass index (BMI) using actual body weight, researchers observed that overweight (25 < BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) patients had numerically lower vasopressin serum concentrations at 72 hours after vasopressin infusion initiation (overweight 51.5 ± 16.5 pmol/L and obese 28.9 ± 7.9 pmol/L) compared with under- or usual-weight (BMI < 25 kg/m^2) patients (69.9 ± 17.5 pmol/L; P = 0.08).[30] The authors also discovered that obese patients had the lowest 28-day mortality, followed by overweight patients, then under- and usual-patients (P = 0.02).[24] In another retrospective analysis of 64 patients receiving vasopressin, primarily at a rate of 0.04 units/minute, investigators observed a significant positive correlation between catecholamine vasopressor requirements at two and four hours and vasopressin dosage adjusted for body weight (correlation coefficient -0.36; P = 0.03 and -0.46; P < 0.01, respectively).[25] In this analysis, the dosage of vasopressin adjusted for body weight ranged from 0.229 to 0.871 micro-units/kg/minute. However, in a retrospective, single-center study of 40 medical ICU patients with septic shock receiving fixed-dose vasopressin, researchers found no correlation between body weight and change in MAP one hour after vasopressin initiation.[26] Although a significant correlation between BMI and change in MAP at six hours was seen in patients with a BMI ≥ 30 kg/m^2 (correlation coefficient r = –0.951; P =0.0009); this was not seen at one or 12 hours (r = –0.487, P = 0.24 and r = –0.243, P = 0.53, respectively).

In the largest retrospective cohort study (n = 938) evaluating this correlation to date, researchers showed that adjusting vasopressin dosing based on weight and BMI did not affect vasopressor requirements or change in MAP.[27] Weight-based vasopressin dosing did not affect mechanical ventilation duration, ICU-free days, or mortality. This confirmed the results of a previous analysis performed by the same authors.[28] Data are conflicting regarding vasopressin weight-based dosing, particularly in overweight and obese patients. Currently, it may be most appropriate not to exceed studied vasopressin dosages in these patients.

VASOPRESSIN DISCONTINUATION IN RESOLVING SEPTIC SHOCK

Patients in early septic shock who have been resuscitated and stabilized adequately transition to the maintenance phase.[29] In the maintenance phase, appropriate vascular tone is maintained with sufficient intravascular volume and vasoactive support. Eventually, an inflection point is reached when endogenous restoration of vascular tone and cardiac function begin to return close to baseline, signaling transition into the recovery phase of septic shock.[30] However, this transition occurs at different time points for patients and often is dependent on patient- and treatment-specific factors, including time to achieve and maintain adequate end-organ perfusion, appropriateness of source control, and antimicrobial therapy.[8,31-33] Intravenous vasopressors are titrated down and, as able, discontinued during the recovery phase, which often necessitates a decision of whether norepinephrine or vasopressin is most appropriate as the final vasopressor for hemodynamic support.[7,34-38]

The authors of a recent systematic review and meta-analysis evaluated the effects of penultimate discontinuation of vasopressin or norepinephrine

in critically ill adults with resolving septic shock.[39] Penultimate discontinuation of norepinephrine compared to vasopressin resulted in a lower incidence and odds of clinically significant hypotension in the meta-analyses at the patient and study level. The difference in hypotension did not translate into differences in the short-term mortality or length of stay in the ICU and hospital from vasopressor discontinuation. In the largest study included in the meta-analysis (n = 585), researchers actually observed a similar incidence of hypotension within 24 hours of penultimate vasopressor discontinuation (vasopressin 55% vs. norepinephrine 50%, $P = 0.28$).[37] However, the four other retrospective, cohort studies supported the hypothesis that penultimate discontinuation of vasopressin resulted in a greater incidence of clinically significant hypotension.[7,34-36] There were no standard practices for vasoactive agent discontinuation in the studies. Additionally, a high degree of heterogeneity existed between studies, although this was mitigated in the meta-analysis through the use of random effects modeling.[39] The only other outcomes that appeared to be different between groups were the durations of vasopressin and norepinephrine infusions, with the penultimately discontinued agent having a shorter infusion duration.

The duration of septic shock and restoration of the vasopressinergic system appear to be two factors that affect the likelihood of hypotension development following vasopressin discontinuation. In the largest study, researchers observed that penultimate discontinuation of vasopressin was independently associated with an increased hypotension risk with a time-varying effect that decreased over time, suggesting earlier vasopressin discontinuation was more likely to result in hypotension.[37] This phenomenon also was observed when data from two other observational cohort studies were combined and stratified by vasopressin duration of less than or greater than 48 hours.[33,35,40,41] The hypothesis that hypotension resulted because the vasopressinergic system was not restored adequately this early in septic shock was tested in a randomized, controlled trial of vasoactive agent discontinuation practices.[38] Copeptin was measured in patients who discontinued vasopressin or norepinephrine in the maintenance or resolving phase of septic shock. Patients who had an elevated serum copeptin concentration were less likely to develop hypotension, suggesting restoration of the vasopressinergic system activity could be used to predict the likelihood of hypotension development. Additionally, vasopressin was weaned off rather than discontinued from the treatment dose (e.g., 0.03 or 0.04 units/minute) in the two studies in which researchers did not observe greater hypotension with penultimate vasopressin discontinuation.[38,39] This practice may be an indirect method for stress-testing restoration of the vasopressinergic system and tolerance for vasopressin discontinuation. In the absence of clinical benefit beyond possibly reduced hypotension development with penultimate norepinephrine discontinuation and the rising cost of vasopressin, weaning off vasopressin before discontinuing norepinephrine during the resolving phase of septic shock may be prudent.[42]

CONCLUSION

Norepinephrine remains the first-line vasopressor in septic shock, although vasopressin may be initiated with potential benefits associated with earlier initiation. Vasopressin dosages may exceed 0.03 units in refractory septic shock, although benefits may not outweigh risks in some patients. Additionally, vasopressin may be titrated to an effect in many patients and weaned off in patients who do not respond to it or in the resolving phase of septic shock. Weight-based vasopressin dosing does not appear to confer benefits in most weight classifications. Further studies are needed to identify the patient populations that would benefit most from vasopressin use. ■

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ABSTRACT & COMMENTARY

Temperature Trajectories to Find Sepsis Subphenotypes

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Dr. Sharma reports no financial relationships relevant to this field of study.

SYNOPSIS: The authors of this study used development and validation cohorts to retrospectively identify temperature trajectories over the first 72 hours from presentation in the setting of sepsis. Patients presenting with hyperthermia that resolved quickly (within the first 24 hours) had lower mortality compared to those with slow resolution or those presenting with hypothermia.

SOURCE: Bhavani SV, Carey KA, Gilbert ER, et al. Identifying novel sepsis subphenotypes using temperature trajectories. *Am J Respir Crit Care Med* 2019;200:327-335.

The authors of this study attempted to identify subphenotypes of sepsis based on the presenting temperature in the emergency department (ED) and the subsequent trajectory of the temperature curve over 72 hours. Patients with sepsis were selected if a blood culture order had been placed and intravenous antibiotics administered within 24 hours of presentation to the ED, defined as the time of first vital signs. Group-based trajectory modeling was used in the development cohort to assign groups based on temperature trajectories within the first 72 hours of data. Group-based trajectory modeling allows for the assessment of individual temperature patterns over time and then assigns individuals to the trajectory group with the highest membership probability. The statistical output computes groupings based on the temperature curve over time as well as individual probabilities of belonging to a specific group. Mean, maximal, and minimal temperatures were computed as well. Temperature measurements were standardized based on mean and standard deviation measurements to enable comparisons. Logistic regression was performed, with temperature trajectory grouping being the predictor variable and mortality being the outcome variable. A fever ("hyperthermia") was defined as a temperature of > 38° C and hypothermia was defined as a temperature below 36° C.

The authors identified four different subphenotypes in the development cohort based on body temperature trajectory: 1) hyperthermic, slow resolvers (HSR); 2) hyperthermic, fast resolvers (HFR); 3) normothermic (NT); and 4) hypothermic (H). Members assigned to the HSR group presented with a fever and had no substantial change in temperature over the first 24 hours. This group also had the highest mean, maximal, and minimal temperatures during the first 72 hours. Those assigned to the HFR group presented with hyperthermia and were more likely to have their temperatures drop close to normal within the first 24 hours. Individuals assigned to the NT group remained so during the 72 hours of observation, whereas individuals assigned to the H, or hypothermic, group presented with hypothermia and stayed hypothermic for the 72-hour observation period. The temperature curves for both the development cohort and the validation cohort were remarkably similar.

The authors discovered significant mortality differences among the four groups. Logistic regression in the validation cohort revealed higher odds of mortality among those in the HSR (odds ratio [OR], 2.15; 95% confidence interval [CI], 1.77-2.61) and H (OR, 1.68; 95% CI, 1.44-1.96) groups compared to those more likely to fall in the NT group. Membership in the HFR group was protective (OR, 0.55; 95% CI, 0.44-0.68). Fever was more common in survivors, and temperature variability was higher in non-survivors compared with survivors. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were higher in the hyperthermic groups, as were the proportion of patients with leukocytosis, attesting to immune upregulation in the hyperthermic groups. Within the hyperthermic groups, ESR and CRP, as well as the proportion of patients with leukocytosis, were higher in the HSR group compared to the HFR group. Hypothermic patients had the lowest ESR and CRP levels and the highest lactate and creatinine of the four groups. Furthermore, the hypothermic group had the highest proportion of patients requiring vasopressors (8.4%) and were the most likely to be exposed to either prednisone or methylprednisolone.

■ COMMENTARY

This is an interesting study that allows for consideration of temperature trajectories over time to be used to predict septic patients who may do poorly. The strength of this study lies in the large number of patients in both the development cohort and the validation cohort, as well as a tight correlation of temperature resolution curves over 72 hours in each cohort (derivation and validation) described.

The statistical technique applied to both the development and validation cohorts assigns a probability of membership of the individuals' temperature trends to a certain group and, therefore, is not a comparison of groups. With this in mind, this study drives home the importance of assessment of a trend and not an individual temperature. For example, transient hypothermia (temperature < 36° C) was fairly common in the development cohort; 81% of patients developed one episode during the observed 72 hours. The cohorts included all patients admitted to two different institutions. While a separate cohort of critically ill patients is not identified, the analysis controlled for severity of illness and, therefore, incorporates those admitted directly to the intensive care unit (ICU) from the ED. However, the results of this study cannot be applied to patients admitted to the ICU from the floor, for example. In an attempt to homogenize populations, the authors of the study incorporated only those patients presenting to and being treated for an infection in the ED. Within this framework, patients more likely to be in the HFR group had the least exposure to vasopressors and lower mortality compared to those more likely to be in the hypothermic trajectory group, which had the highest exposure to vasopressors and higher mortality.

Recent literature has begun to assess the utility of signs assessed on physical examination of critically ill patients. For example, the authors of one study found that a fluid resuscitation strategy that targeted normalization of capillary refill time (CRT) was non-inferior to a strategy that used a lactate-driven strategy and even may have been better among those with lower severity of illness scores.[1] The Simple Intensive Care Studies-I (SICS-I) group investigators focused on the predictive value of clinical signs acquired within the first 24 hours of ICU admission with respect to outcomes.[2] Prolonged CRT and low peripheral temperature may predict the development of acute kidney injury (AKI).[2] A particular combination of physical findings, including low central temperature, reduced urine output, and higher respiratory rate, may predict mortality as well as the APACHE score.[3]

The one question that the study reviewed here does not address is how temperature trajectory correlates and/

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or clusters with other parameters commonly assessed in tandem, such as blood pressure, respiratory rate, oxygenation indices, and possibly urine output trends over time. Based on the results of this study, it appears reasonable to investigate more aggressively those hyperthermic patients who fail to defervesce (i.e., those who could be in the HSR group) in the first 24 hours and look for persistent sources of infection when a source is apparent (e.g., pneumonia leading to meningitis or endocarditis). Similarly, patients who present with hypothermia and continue to be hypothermic over the course of hospital admission require aggressive evaluation given the increased odds of mortality. Further studies to assess how temperature trajectory interacts with the trajectory of other vital signs may allow for further subphenotyping of patients presenting with sepsis. ■

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CME/CE QUESTIONS

1. Penultimate discontinuation of vasopressin rather than norepinephrine has been associated with which outcome?
a. Decreased intensive care unit length of stay
b. Decreased hospital length of stay
c. Lower odds of clinically significant hypotension
d. Reduced duration of intravenous vasopressors

2. Which one of the following groups had the highest in-hospital mortality when assessed with respect to temperature trajectory over the first 72 hours?
a. Hyperthermic slow resolvers
b. Hyperthermic fast resolvers
c. Hypothermic group
d. Normothermic group

3. In the Bhavani study, which of the following statements is true?
a. Patients with persistent hypothermia were more likely to require vasopressor support compared to those with hyperthermia.
b. Patients with persistent hypothermia were less likely to have received steroids compared to those with hyperthermia.
c. Transient hypothermia is fairly uncommon in the setting of sepsis.
d. Hypothermic patients were more likely to have a lower lactate compared to those with hyperthermia.

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.