Intensity of Vasopressor Therapy for Septic Shock and the Risk of In-Hospital Death

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Brief Report

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ABSTRACT

Context. Given the high mortality of 30-60% associated with septic shock, distinguishing which patients do or do not have a reasonable chance of surviving with aggressive treatment could help clinicians and families make informed decisions.

Objectives. To determine if intensity of vasopressor therapy accurately predicts in-hospital death.

Methods. This observational cohort study analyzed in-hospital mortality as a function of intensity of vasopressor therapy in a consecutive series of adults with septic shock treated over a 4-year period. Receiver operating characteristic (ROC) curve analysis assessed the overall strength of the intensity-mortality relationship.

Results. A total of 808 patients with septic shock experienced an in-hospital death rate of 41.0% (331/808) (95% confidence interval, 38.5% to 44.5%). The greater the peak number of vasopressors required, the higher the death rate, which reached 92.3% (12/13) (95% CI, 79.4% to 100.0%) when 3 different pressors were being infused at full dose. The ROC curve analysis revealed that number of simultaneous vasopressors and vasopressor dose load performed equally well in predicting death or survival.

Conclusions. When a standard full dose of a vasopressor fails to normalize blood pressure in a patient with septic shock, escalation begins to yield diminishing returns as the dose and multiplicity of agents approach practical upper limits. While it is not possible to specify a precise cutoff for limiting vs. intensifying therapy, a mortality of 80% or higher—characterized by 2 or more concurrent vasopressors at full dose—should prompt shared decision making with the patient's family.

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Key Words: Vasoconstrictor Agents; Hospital Mortality; Cohort Studies; Septic Shock; Critical Care; Decision Making

Running Title: Vasopressor Therapy and In-Hospital Death
Introduction

Sepsis is a pathologic, systemic response to infection. When severe, it can cause end-organ dysfunction characterized by oliguria, thrombocytopenia, coagulopathy, and elevated serum lactate levels. Septic shock, the most severe form of sepsis, occurs when hypotension persists despite appropriate fluid resuscitation. The incidence of septic shock is approximately 31 cases per 100,000 population per year (1), accounting for about 8% of all admissions to an intensive care unit (2). Mortality ranges from 30 to 60% (3-8).

When fluid resuscitation alone fails to restore adequate blood pressure, the catecholamine agonists norepinephrine, dopamine, epinephrine, and phenylephrine may be administered, usually starting with norepinephrine as the recommended first-line vasopressor agent (9). In patients with refractory hypotension, vasopressin may be added on grounds that patients with septic shock frequently manifest low serum vasopressin concentrations (10). Since it is difficult, in practice, to assess which patients are vasopressin-deficient, an empirical approach to this therapy is typical.

Given the high mortality associated with septic shock, a method of distinguishing patients who do or do not have a reasonable chance of surviving with aggressive treatment could help clinicians and families weigh the options and make informed decisions. Anecdotal observations at our institution and a few published reports (11-13) have suggested that the chance of surviving septic shock decreases as the intensity of vasopressor therapy needed to treat the condition escalates.

The present observational cohort study examined in-hospital mortality as a function of therapeutic intensity by analyzing vasopressor use and survival status in a consecutive series of adult patients with septic shock who were admitted to Winthrop University Hospital over a four-
year period. We expected to observe increasing mortality with higher doses and multiplicity of vasopressors used to treat refractory septic shock. We also hypothesized the existence of a "futility threshold" above which further escalation of therapy would offer so little hope that continued vasopressor infusion would probably not be in the patient's best interests.

The study was approved by the hospital's Institutional Review Board, which waived the need for informed consent.

Methods

Setting and Patients

Winthrop University Hospital is a 591-bed, university-affiliated tertiary care teaching hospital located on Long Island, New York. The present study included all adult patients (age ≥ 18 years) with a principal or secondary diagnosis of septic shock who were admitted to the hospital between January 1, 2009 and December 31, 2012. If a patient had multiple admissions with a diagnosis of septic shock, only one of these admissions—selected by a random number generator—was included. Patients receiving intravenous vasopressor therapy for septic shock are usually treated in one of the hospital's five adult intensive care units: a medical intensive care unit, a coronary care unit, a general surgical intensive care unit, a cardiothoracic intensive care unit, or a neurology/neurosurgical intensive care unit.

Data Collection

Patients with septic shock (ICD-9 code 785.59) (14) were identified through a query of the hospital's administrative data system. If a patient had one or more pharmacy records indicating an order for a vasopressor, we manually reviewed the patient's hospital medical record to confirm the diagnosis of septic shock and obtain details of vasopressor administration. If this review revealed that the diagnosis had been miscoded as septic shock when the actual cause of shock was not sepsis (e.g., cardiogenic or hypovolemic shock), the patient was excluded.
The following information was recorded from the nurse’s medication log for each vasopressor a patient received: name of drug, start date and time, stop date and time, and maximum dose given. The patient's age, sex, admitting service, length of stay in the hospital, and survival status (survived to discharge or died in the hospital) were obtained from the hospital's administrative data system.

Analysis

To analyze intensity of vasopressor therapy, two alternative measures of therapeutic intensity were applied: (1) number of different vasopressors administered concurrently at full dose, and (2) vasopressor dose load. For the first measure, 20 mcg/min of norepinephrine was considered to be a "full dose." Likewise, 10 mcg/min of epinephrine, 20 mcg/kg/min of dopamine, 180 mcg/min of phenylephrine, and 4 unit/hr of vasopressin were considered to be full doses of these drugs. Although the medical literature does not specify explicit upper limits on vasopressor doses for the treatment of septic shock (15), the amounts listed above correspond to the customary maximum doses used to treat this condition at our hospital.

The second measure of therapeutic intensity combines the individual doses of different concurrent vasopressors to produce a composite vasopressor dose load. This measure is based on an established therapeutic equivalence formula that converts doses of epinephrine, dopamine, and phenylephrine into norepinephrine dosage equivalents to yield a total dose load expressed in mcg/min (7,16). We adapted this formula to incorporate vasopressin by referring to observations made in the Vasopressin and Septic Shock Trial (VASST) (7). In that study, the introduction of 1.8 units/hr of vasopressin in a group of patients receiving norepinephrine bitartrate reduced the required dose of norepinephrine by approximately 10 mcg/min. It follows that 1 unit/hr of vasopressin is equivalent to 5.6 mcg/min of norepinephrine (10/1.8 = 5.6). We
therefore used the multiplier 5.6 to convert vasopressin in the following expanded version of the therapeutic equivalence formula:

\[
\text{Vasopressor Dose Load} = \text{norepinephrine (in mcg/min)} + 0.5 \times \text{dopamine (in mcg/kg/min)} + \\
\text{epinephrine (in mcg/min)} + 0.1 \times \text{phenylephrine (in mcg/min)} + 5.6 \times \text{vasopressin (in units/hr)}
\]

While the first measure of therapeutic intensity considers only vasopressors administered at full dose, the second measure accounts for all vasopressors infused at any dose. A patient given 20 mcg/min norepinephrine with 15 mcg/kg/min dopamine, for example, would be receiving 1 vasopressor at full dose, or a vasopressor dose load of 27.5. For either measure, a vasopressor had to be infused for at least 1 hour to be counted in the analysis. However, patients with a diagnosis of septic shock who did not receive vasopressor therapy were included. For these patients, fluid resuscitation alone had often been successful at normalizing the blood pressure. These patients were assigned \textit{number of vasopressors} = 0 and \textit{dose load} = 0 in the analysis.

For each patient, we calculated the peak number of concurrent vasopressors at full dose, as well as the peak vasopressor dose load based on the formula. We then analyzed in-hospital mortality as a function of peak number of vasopressors (≥0, ≥1, ≥2, ≥3) and peak vasopressor load (≥0, ≥20, ≥40, ≥60, ≥80, ≥90). To investigate the possible effect of age on the intensity-mortality relationship, we repeated these analyses after separating patients into the following age strata: 18-49, 50-59, 60-69, 70-79, and 80+.

The primary statistical analysis consisted of computing death rates with confidence intervals. In addition, receiver operating characteristic (ROC) curve analysis was used to assess the overall strength of the intensity-mortality relationship and accuracy of the intensity measures as predictors of in-hospital death. For a given measure, ROC curve analysis calculates the
sensitivity and specificity values associated with all possible cutoff points and computes the area under the ROC curve to indicate the measure's overall predictive ability.

**Results**

Over the 4-year study, 808 adults were either admitted to the hospital with septic shock or developed the condition during hospitalization (Table 1). They experienced an overall in-hospital death rate of 41.0% (331/808) (95% confidence interval, 38.5% to 44.5%). The greater the peak number of vasopressors required, the higher the death rate, which reached 92.3% (12/13) (95% CI, 79.4% to 100.0%) when 3 different pressors were being infused at full dose (Fig. 1a). Death rate was also positively associated with peak vasopressor dose load up to about 40 mcg/min, at which point mortality leveled off at approximately 80-90% (Fig. 1b). Similar mortality vs. intensity relationships were observed within each age stratum (Fig. 2).

Note that a dose load of 60 corresponds to the infusion of 3 concurrent vasopressors at full dose, since 20 mcg/min norepinephrine represents a full dose of that drug. Some patients received even higher loads because the clinician chose to administer at least one vasopressor above the "full dose." For example, one patient received 35 mcg/min norepinephrine together with 16 mcg/kg/min dopamine and 8 units/hr vasopressin, yielding a dose load of 88. The first and last vasopressors were infused above their customary upper limits.

The ROC curve analysis confirmed the positive association between intensity and mortality and determined that each intensity measure was moderately accurate in predicting in-hospital death or survival: the area under the ROC curve was 0.70 for number of concurrent pressors (p<0.0001) and 0.72 for vasopressor dose load (p<0.0001). The small difference between the two areas is not statistically significant (p=0.15) (17), indicating that the two measures offer equally good predictions.
Discussion

Previous studies of vasopressor use and outcome in intensive care settings have reported mixed results. Three studies found very low survival rates—under 10%—among patients receiving a high dosage or multiple concurrent administration of vasopressors (n=64 [11], n=66 [12], and n=166[13]), while two other studies reported that dosage did not have prognostic significance (n=1543 [18] and n=113 [19]).

The present investigation of 808 patients with septic shock revealed a clear positive relationship between intensity of vasopressor therapy and in-hospital mortality. Overall, 41% of these patients died in the hospital, but mortality exceeded 90% in patients receiving 3 or more concurrent pressors at full dose or a combination of drugs that yielded a vasopressor dose load equivalent to 90 mcg/min norepinephrine or greater. ROC curve analysis demonstrated that the two measures of therapeutic intensity performed equally well in predicting death or survival. Since the vasopressor count is much easier to use than the dose load formula, which requires a calculation, clinicians may prefer mortality statistics based on number of vasopressors.

To calculate a patient's vasopressor dose load, we modified a previously published therapeutic equivalence formula that incorporated the most frequently used catecholamines (7,16). The original formula did not account for vasopressin, because it was not widely used when the formula was developed and because it is not a catecholamine. Since then, vasopressin has become commonplace in the treatment of septic shock refractory to first-line vasopressors, so it was necessary for us to update the formula to account for its widespread use. Although current guidelines recommend use of vasopressin at a fixed dose as an adjunctive agent (9), at our institution this drug is sometimes used in escalating doses. In such cases, it is functioning in a manner analogous to adrenergic agents that exhibit a dose-response relationship to blood
pressure. To reflect this reality, it seemed reasonable to include vasopressin in the dose load formula.

An ideal clinical predictor would exhibit both high sensitivity (few false-negatives) and high specificity (few false-positives), but most real predictors have to sacrifice one or the other of these, depending on the context. Predicting the outcome of septic shock based on a particular vasopressor intensity cutoff necessitates tolerating low sensitivity in order to achieve sufficiently high specificity. For example, a cutoff of 2 concurrent vasopressors at full dose produces a high specificity (95.8%) and positive predictive value (80.6%) at the expense of a low sensitivity (25.1%) and negative predictive value (35.2%). (These 4 percentages can be derived from data presented in Fig. 1a). The asymmetry is appropriate in the present context. The potential harm caused by an erroneous prediction of death that leads to premature discontinuation of treatment—a false-positive—far outweighs the potential harm caused by an erroneous prediction of survival that results in futile continuation of treatment—a false-negative. The ratio of harms caused by the two errors is not infinite, however. At some point, the balance must favor switching to comfort care only.

Our investigation demonstrated a higher likelihood of death with increasing vasopressor requirements. Patients requiring 2 or more vasopressors at full dose experienced a mortality of 80.6%. A total of 103 patients, or about 1 in 8, fell into this category (Fig. 1a). It may not be possible to specify a precise "futility threshold," since patients and families interpret mortality data in light of many individualized medical, psychological, and social factors. In one situation, a family might favor switching to palliative care when the patient has a 15% chance of survival. In a different situation, a family might opt to escalate therapy when the patient's chance of survival is less than 5%. Nevertheless, knowing the true risk of death in relation to treatment intensity permits informed decision making about further treatments.
Since this was an observational study, the treatment of study patients was not standardized. Our investigation examined vasopressor dosing, but variables we did not measure must also bear upon the probability of death. For example, all patients received fluid resuscitation, but the target varied, reflecting the ongoing debate over the optimal way to assess adequacy of fluid resuscitation: measurement of central venous pressure and venous oxygenation, variability in diameter of the inferior vena cava measured by bedside ultrasonography, or pulse pressure or stroke volume variability (20, 21). While acknowledging this limitation, we do not believe this type of variability in treatment would substantially alter the study’s characterization of the vasopressor intensity vs. mortality relationship.

The risk of death from septic shock increases steadily as the need for vasopressor therapy intensifies. Mortality reaches 80 to 90 percent when 2 or more pressors have been administered at full dose. This observation provides a simple framework for clinicians to use in counseling families about continuing versus limiting interventions in the intensive care unit. While the study did not yield an unequivocal treatment futility threshold, it provides empirical data on the likelihood of survival in septic shock as a function of vasopressor treatment intensity, reducing guesswork and conjecture and facilitating informed decision making.

Disclosures and Acknowledgments

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References


**Figure 1**—In-hospital mortality vs. intensity of vasopressor therapy

**Figure 1 Legend:** Therapeutic intensity was measured using (a) peak number of concurrent vasopressors at full dose, or (b) peak vasopressor dose load. Mortality rates refer to patients who received at least the indicated number of vasopressors or dose load. Error bars indicate 95% confidence intervals.

**Figure 2**—In-hospital mortality vs. intensity of vasopressor therapy, by age group

**Figure 2 Legend:** Mortality rates refer to patients who received at least the indicated number of vasopressors or dose load.
Table 1

Characteristics of study patients. N=808

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<th>Gender</th>
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<table>
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<th>Age</th>
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<tr>
<td>18-49</td>
<td>55 (6.8%)</td>
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<td>50-59</td>
<td>82 (10.1%)</td>
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<tr>
<td>60-69</td>
<td>149 (18.4%)</td>
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<tr>
<td>70-79</td>
<td>205 (25.4%)</td>
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<tr>
<td>80+</td>
<td>317 (39.2%)</td>
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<table>
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<th>Length of stay</th>
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<th>Admitting service</th>
<th>Count (Percentage)</th>
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<tr>
<td>Medicine</td>
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<tr>
<td>Surgery</td>
<td>129 (16.0%)</td>
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<tr>
<td>Other or unknown</td>
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<table>
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