Background Whether or not norepinephrine infusions for support of hemodynamic status in patients with septic shock should be weight based is unknown. This situation is particularly pertinent in patients who are extremely overweight or obese.

Objective To compare dosing requirements and effect of norepinephrine on blood pressure in obese and non-obese patients with septic shock.

Methods In a retrospective cohort study, data on adult patients with septic shock who received norepinephrine infusion for support of hemodynamic status in a tertiary care, academic medical center were analyzed. Patients were categorized as obese (body mass index ≥ 30) or nonobese (body mass index < 30). The primary outcome was dosing requirements of norepinephrine at 60 minutes after the start of the infusion. The secondary outcome was the log-transformed ratio of mean arterial pressure to norepinephrine.

Results The final cohort consisted of 100 obese and 100 nonobese patients. Mean norepinephrine infusion rate at 60 minutes was 0.09 (SD, 0.08) µg/kg per minute in the obese group and 0.13 (SD, 0.14) µg/kg per minute in the nonobese group (P = .006). The non–weight-based dose at 60 minutes was 9 µg/min in obese patients and 8 µg/min in nonobese patients (P = .72). The log transformed mean arterial pressure to norepinephrine ratio at 60 minutes was 2.5 (SD, 0.9) in obese patients and 2.5 (SD, 0.8) in nonobese patients (P = .54).

The Surviving Sepsis Campaign international guidelines for the management of severe sepsis and septic shock recommend norepinephrine as the first-choice vasoppressor for patients with fluid-refractory shock. The recommended target for vasopressor therapy is a mean arterial blood pressure (MAP) greater than 65 mm Hg. In clinical trials, both weight-based and non–weight-based dosing of norepinephrine have been used to achieve this target. Similarly, drug information sources provide both weight-based and non–weight-based dosing recommendations. The difference in recommendations between sources often leads to inconsistency in dosing between providers and institutions.

Use of weight-based dosing is based on the assumption that a linear relationship exists between a patient's weight and his or her total norepinephrine requirement. However, pharmacokinetic and pharmacodynamic studies of norepinephrine in patients with septic shock have shown great interpatient variability, low correlation between dose and plasma concentration, and low correlation between plasma concentration and clinical response. In addition, weight is often estimated in critical care, and the estimate may not be accurate. During hospitalization, documentation of a patient's weight may be changed to correct an erroneous estimate made at admission or to account for real changes due to fluid accumulation. Changes in the weight used for weight-based dosing of norepinephrine in these circumstances could lead to arbitrary changes in the total amount of drug delivered to patients that are unrelated to hemodynamic requirements. Thus, the need for weight-based dosing of norepinephrine in these patients is unclear, and such dosing may be a source of medication errors due to logistical reasons. Use of weight-based dosing is particularly a concern for patients who are obese.

Current guidelines do not provide any recommendations on weight-based or non–weight-based dosing of norepinephrine. For logistical reasons, a non–weight-based dosing strategy with titration to response may be preferred. However, the need for weight-based dosing is unclear. The objective of this study was to compare dosing requirements for norepinephrine in obese and nonobese patients with septic shock. We hypothesized that total dosing requirements and effect on MAP would be similar between the 2 groups, suggesting that a non–weight-based dosing strategy is appropriate.

**Materials and Methods**

**Study Population**

This retrospective cohort study was an analysis of data on patients admitted to the medical and surgical-trauma intensive care units (ICUs) at the University of Arizona Medical Center, Tucson, Arizona, a tertiary care, academic medical center. The study was approved by the hospital site review authority and the university's institutional review board. Adult ICU patients with septic shock who received norepinephrine as the sole vasopressor for unstable hemodynamic status for at least 1 hour and were admitted during the period July 2009 through June 2012 were included in the study. The medical center has no standard protocol for norepinephrine dosing. Patients were excluded if they received another vasopressor within 1 hour of the start of the norepinephrine infusion. The purpose of this exclusion was to minimize any possible effect of other vasopressors on norepinephrine requirements. Also, patients were excluded if they were less than 18 years old or if the primary treatment team was not the medical or surgical ICU team.

**Definitions**

Patients were categorized as obese or nonobese on the basis of their body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. Patients with a BMI of 30 or higher were considered obese; those with a BMI less than 30 were categorized as nonobese. Septic shock was defined as unstable hemodynamic status despite fluid administration and proven or suspected infection in conjunction with at least 2 of the following criteria for systemic inflammatory response: heart rate greater than 90/min, body temperature less than 36°C (96.8°F) or greater than 38°C (100.4°F), or a white blood cell count less than 4000/µL or

---

**About the Authors**

John J. Radosevich is a clinical pharmacist, critical care, Pharmacy Department, St Joseph’s Hospital and Medical Center, Phoenix, Arizona. Asad E. Patanwala is an associate professor and Brian L. Erstad is a professor and department head, Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, Arizona.

Corresponding author: Asad E. Patanwala, PharmD, 1295 N Martin Ave, PO Box 210202, Tucson, AZ 85721 (e-mail: patanwala@pharmacy.arizona.edu).
greater than 12 000/µL, or the presence of more than 10% bands. Unstable hemodynamic status was defined as systolic blood pressure less than 90 mm Hg or MAP less than 65 mm Hg. These definitions are consistent with published definitions and definitions used in previous studies on the effects of body mass on hemodynamic response to vasopressor therapy.1,8-10 In order to determine the effect of body mass on hemodynamic response to vasopressors, the 2 measurements were combined and log-transformed into a single variable: the log MAP:NE ratio. This combined variable was used in a previous study11 because MAP and norepinephrine dosing are interrelated. This measure is meaningful because the adequacy of norepinephrine dosing is a function of MAP and the ratio reflects the combined effect of both the vasopressor and blood pressure.

Data Collection

The pharmacy computer system was used to identify patients who received norepinephrine during the study period. Consecutive patients were evaluated for inclusion. Because nonobese patients were expected to outnumber obese patients, a blocking scheme was used to obtain an equal number of patients in the obese and nonobese groups during similar periods. The purpose of this step was to minimize bias and to ensure that obese and nonobese patients would be included from similar periods. Potential patients were selected in chronological order in blocks of 10. The procedure was to enroll 5 patients in each group for a block of 10 total patients. For example, if 5 eligible nonobese patients were included before 5 obese patients, then nonobese patients were skipped until 5 obese patients were identified and included. Once the block of 10 was completed, the process was continued until 100 patients were included in each group.

The patients’ medical records were accessed, and the following data were collected for each patient: age, sex, height, weight, BMI, primary service, corticosteroid use, and source of infection. Nurses used electronic bed scales to obtain patients’ weight. Laboratory data collected included serum levels of creatinine and cortisol, pH, hematocrit, and white blood cell count. MAP values were obtained via arterial catheter measurements. Fluids administered in the 6 hours before and the 6 hours after the start of the norepinephrine infusion were noted. Fluid replacement was not standardized at the medical center during the study period. Severity of illness was measured by calculating the Sequential Organ Failure Assessment score, and comorbid conditions were assessed by using the Charlson Comorbidity Index. All laboratory data and Sequential Organ Failure Assessment scores were obtained at the time the norepinephrine infusion was started, which was also the time of admission for most patients.

End Points

The primary outcome measure was the norepinephrine infusion rate 60 minutes after the start of administration of the drug for treatment of septic shock, when titrated to a goal MAP of 65 mm Hg or greater. This goal MAP is part of the institutional protocol. The secondary outcome measure was a comparison of the log MAP:NE ratio at 60 minutes after the start of the infusion. These outcome measures are consistent with those of previous studies11,12 on the effect of vasopressors on MAP.

Statistical Analysis

Baseline, demographic, and outcome variables of obese and nonobese patients were compared. Categorical variables were compared by using the Fisher exact test. Continuous variables were analyzed by using the Mann-Whitney test. A nonparametric test was used because the variables did not meet the assumption of normality. The norepinephrine infusion rates and log MAP:NE ratios were compared between groups by using an unpaired t test. A linear regression analysis was performed to determine the effect of weight on log MAP:NE ratios at 60 minutes, after adjustments for baseline MAP. Data were reported as percentages, medians and interquartile ranges (IQRs), or means and standard deviations, as appropriate. A power analysis was conducted by using the norepinephrine infusion rates from a previous investigation13. For an infusion rate of 0.1 µg/kg per minute, an SD of 0.07, an effect size of 0.03 µg/kg per minute, power of 80%, and α = .05, the estimated sample size was 87 patients in each group. This number was increased to 100 patients in each group to increase power. A 2-sided α = .05 was used for all analyses. All analyses were performed by using Stata 13 software (StataCorp LP).

Results

Study Cohort

During the 3-year period studied, 1340 patients received norepinephrine. Of these, 482 were not evaluated because of the blocking scheme for case selection. Of the remaining cases, 658 patients were excluded because they received norepinephrine for an indication other than septic shock or they received norepinephrine under the care of a service...
other than the medical or surgical ICU team. Thus, a total of 200 patients were included in the final study cohort (100 obese and 100 nonobese).

Overall, the median age was 61 years (IQR, 53-72), and 54% were men. The majority of patients were white (62%) or Hispanic (28%). Most patients were under the care of the medical ICU (90%). Also, a large proportion of patients (61%) were receiving mechanical ventilation at the time infusion of norepinephrine began. The median Sequential Organ Failure Assessment score was 8 (IQR, 6-10), and the median Charlson Comorbidity Index was 2 (IQR, 1-4). The most common presumed infection was pneumonia (56%). Demographic comparisons between obese and nonobese patients are reported in Table 1. Clinical characteristics are reported in Table 2. No significant baseline differences were detected between the groups. The only exception was that patients in the nonobese group were slightly older (P<.001), with a median age of 65 years (IQR, 56-77 years), than were patients in the obese group, whose median age was 58 years (IQR, 50-66 years).

**Table 1** Baseline demographics\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obese</th>
<th>Nonobese</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>58 (50-66)</td>
<td>65 (56-77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>101 (89-119)</td>
<td>66 (59-77)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Body mass index, median (IQR)</td>
<td>36 (32-42)</td>
<td>24 (21-26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>49</td>
<td>58</td>
<td>.26</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>.70</td>
</tr>
<tr>
<td>White</td>
<td>63</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>29</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Type of intensive care unit</td>
<td></td>
<td></td>
<td>.64</td>
</tr>
<tr>
<td>Medical</td>
<td>88</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>12</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>68</td>
<td>54</td>
<td>.06</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
\(^a\) Values in second and third column are percentage of patients unless otherwise indicated in first column.

**Table 2** Clinical characteristics\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obese</th>
<th>Nonobese</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum level of creatinine, mg/dL</td>
<td>1.8 (1.0-3.5)</td>
<td>1.5 (0.9-3.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Cortisol, µg/dL</td>
<td>15.8 (10.0-25.5)</td>
<td>14.7 (11.4-24.2)</td>
<td>.78</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 (7.25-7.40)</td>
<td>7.35 (7.27-7.42)</td>
<td>.18</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>38.5 (27.4-35.9)</td>
<td>31.6 (28.2-37.3)</td>
<td>.23</td>
</tr>
<tr>
<td>White blood cell count, per µL</td>
<td>15.3 (9.4-20.4)</td>
<td>15.4 (9.1-24.4)</td>
<td>.43</td>
</tr>
<tr>
<td>SOFA score</td>
<td>8.0 (6.0-10.0)</td>
<td>8.0 (6.0-10.5)</td>
<td>.57</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>.99</td>
</tr>
<tr>
<td>Source of infection, % of patients</td>
<td></td>
<td></td>
<td>.88</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>54</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Urinary</td>
<td>19</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Skin/skin structure</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Joint</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SOFA, Sequential Organ Failure Assessment.
\(^a\) Values in second and third column are median (interquartile range) unless otherwise indicated in first column.

Norepinephrine Dosing and MAP

Mean MAP at baseline was 54 (SD, 8) mm Hg in the obese group and 56 (SD, 8) mm Hg in the nonobese group (P=.11). At 60 minutes after infusion of norepinephrine began, mean MAP increased to 73 (SD, 11) mm Hg in the obese group and 74 (SD, 14) mm Hg in the nonobese group (P=.48). The initial rate of infusion was 0.07 (SD, 0.21) µg/kg per minute in the obese group and 0.08 (SD, 0.06) µg/kg per minute in the nonobese group (P=.76). At 60 minutes, the infusion rate was 0.09 (SD, 0.08) µg/kg per minute in the obese group and 0.13 (SD, 0.14) µg/kg per minute in the nonobese group (P=.006). The equivalent non–weight-based dose (ie, [micrograms per kilograms per minute] x weight) at 60 minutes was 9 µg/min in the obese group and 8 µg/min in the nonobese group (P=.72). At 60 minutes, the percentage of patients with MAP 65 mm Hg or greater was 81 in the obese group and 72 in the nonobese group (P=.18). In patients with an MAP of 65 mm Hg or less (n = 153), the rate at 60 minutes was 0.09 (SD, 0.08) µg/kg per minute in the obese group and 0.12 (SD, 0.13) µg/kg per minute in the nonobese group (P=.05). The equivalent non–weight-based dose at 60 minutes in this subgroup was 9 µg/min in the obese group and 8 µg/min in the nonobese group (P=.59).

The cumulative norepinephrine dose at 60 minutes was 481 (SD, 368) µg in the obese group and 458 (SD, 426) µg in the nonobese group (P=.68). The mean log MAP:NE ratio at 60 minutes was 2.5 (SD, 0.9) in the obese group and 2.5 (SD, 0.8) in the nonobese group (P=.54). After adjustments were made for baseline MAP, patients’ weight was not significantly associated with log MAP:NE ratio (P=.97).

Fluids and Medications

Obese patients received 2513 (IQR, 1315-3967) mL of intravenous fluids, and nonobese patients received 2975 (IQR, 2013-4380) mL. These values are equivalent to a weight-based volume of 22 (IQR, 13-38) mL/kg in the obese group and 46 (IQR, 33-66) mL/kg in the nonobese group. Fluid use within 6 hours before infusion of norepinephrine began was
Obese patients with septic shock required a lower weight-based norepinephrine infusion rate than did nonobese patients.

Discussion

The key finding in this study was that obese patients with septic shock required a lower weight-based norepinephrine infusion rate than did nonobese patients. As a result, the non–weight-based doses were similar between groups. Our results suggest that a weight-based dosing strategy may not be necessary and that a non–weight-based dosing strategy can be used even in patients who are obese.

Potential disadvantages are associated with weight-based regimens in critically ill patients. For instance, weight-based dosing can increase the complexity of care and may lead to medication errors.14 This situation is particularly true during nonautomated programming of infusion pumps, which requires an additional step of weight entry and a need for calculation. For instance, if the weight value used in the pump is erroneously changed, then the same infusion rate would result in a different total norepinephrine dose being delivered to the patient. In the ICU, patients experience frequent and often dramatic weight fluctuations, sometimes within a single day. These fluctuations can affect the weight clinicians should program into pumps for weight-based infusions.15 With weights changing so frequently, applying weight-based dosing in the ICU, where a change in weight-based norepinephrine began was also similar in obese and nonobese patients (9% vs 5%, respectively; P = .41). Blood products were used in 16% of obese patients and 18% of nonobese patients (P = .85).

Recent studies16-19 have indicated that the outcomes (ie, hospital mortality) and characteristics (ie, type of underlying infection) of critically ill obese patients differ from those of nonobese patients. These differences may be due to underlying pathophysiological mechanisms or differential use of therapies or suboptimal drug dosing. Optimizing drug dosing is particularly difficult because little is known of the effect of obesity on pharmacokinetics and pharmacodynamics for most drugs.20,21 Package inserts for many medications have weight-based dosing recommendations, but because many clinical trials do not include a large number of obese patients, appropriate dosing in obese patients is often unknown. This lack of information is the case for most of the commonly used vasoactive medications in the ICU, including norepinephrine. Although norepinephrine is titrated to effect, our study provides evidence that weight-based dosing may not be necessary.

An interesting finding in our study was that obese and nonobese patients received similar amounts of fluids. Thus, the weight-adjusted fluid volume was greater in the nonobese patients. This difference may be attributed to the lack of a linear relationship between circulating blood volume and weight.22 Compared with lean body mass, adipose tissue is relatively poorly perfused. Thus, weight-adjusted volume decreases as BMI increases, a finding that may help explain the differences in fluid requirements between our 2 groups. Alternatively, obese patients might have received less fluid than needed and thus could have required more norepinephrine. However, we did not show a higher norepinephrine use in the obese group, suggesting that the patients most likely did receive adequate fluid replacement.

In a study6 of patients with septic shock or trauma who required a catecholamine infusion, norepinephrine was initiated and titrated in increments of 0.1 µg/kg per minute. Plasma levels of norepinephrine were measured several times after the infusion. The results indicated that body weight did not influence pharmacokinetic parameters such as clearance or volume of distribution. If dosing should be based on body weight for norepinephrine, then the following must be true. First, the relationship between dose administered and pharmacokinetic parameters, including concentration of norepinephrine, must be significant. However, we found no correlation between dose and concentration in this study. Second, the relationship between circulating concentrations of norepinephrine and resulting...
effects on MAP must be significant. However, great interpatient variability and unpredictability exist between concentration and MAP.13

Our study has limitations related to the study design. Because it was a retrospective cohort study, we were dependent on accurate documentation in the medical record. The groups were well matched with respect to all demographics, with the exception of age. However, this small difference in age is not considered clinically meaningful. Also, the majority of patients included in the study were admitted to the medical ICU; thus, our results may not be generalizable to patients in surgical or cardiovascular ICUs. Our outcome measures were determined at 60 minutes after the start of the norepinephrine infusion, similar to the methods used in previous studies. Thus, our results should be extrapolated with caution beyond this time frame. Overall, less fluid was administered to the obese group than to the nonobese group. This discrepancy may have confounded norepinephrine requirements. If the obese patients received less fluid, then they would be expected to require more norepinephrine, suggesting that the current infusion rate in that cohort is inflated. However, the total norepinephrine dose was similar in the 2 groups. This finding strengthens our rationale for using a non–weight-based approach, because even though obese patients may have received smaller amounts of fluids than nonobese patients did, the obese group did not require a higher dose of norepinephrine, as would be the case if weight-based dosing were used.

Compared with nonobese patients, obese patients have lower weight-based norepinephrine dosing requirements for septic shock. This difference translates to similar total norepinephrine dosing requirements to achieve MAP goals. Consequently, a non–weight-based dosing strategy with titration to effect may be appropriate in obese patients with septic shock. Because of the ease of use and logistical advantages, non–weight-based dosing is appealing for critically ill patients. Future prospective studies are needed to compare weight-based vs non–weight-based dosing strategies for norepinephrine.

ACKNOWLEDGMENTS
This study was conducted at the University of Arizona Medical Center, Tucson, Arizona.

FINANCIAL DISCLOSURES
None reported.

eLetters
Now that you’ve read the article, create or contribute to an online discussion on this topic. Visit www.ajcconline.org and click “Submit a response” in either the full-text or PDF view of the article.

REFERENCES

To purchase electronic or print reprints, contact American Association of Critical-Care Nurses, 101 Columbia, Aliso Viejo, CA 92656. Phone, (800) 899-1712 or (949) 362-2050 (ext 532); fax, (949) 362-2049; e-mail, reprints@aacn.org.