# Early May Be Better: Early Low-Dose Norepinephrine in Septic Shock

In this issue of the *Journal*, Permpikul and colleagues (pp. 1097–1105) report on a phase 2 randomized controlled trial (RCT) of early low-dose norepinephrine (NE) in septic shock (1). Arguably the most important finding from studies of antibiotic timing (2, 3) and early goal-direct therapy (3, 4) is that early treatment of septic shock is beneficial. At first, the design may appear odd, but a close reading reveals a neat design that allows early testing of the intervention (early low-dose NE), allowing separation of the treatment groups without denying "standard" care and without forcing any patients to receive "late" NE.

The authors randomized patients to early low-dose NE ($n = 155$) or placebo infusion ($n = 155$) plus standard care, which included open-label vasopressors. NE study drug dose was weight-based infused via peripheral intravenous lines in many cases until a dose of 0.05 μg/kg/min was achieved (e.g., 3 μg/min in a 60-kg patient), plus open-label vasopressors and fluid resuscitation, and NE dose was unchanged for 24 hours. The primary outcome was control of shock defined by a composite of mean arterial pressure (MAP) greater than 65 mm Hg plus either urine output greater than 0.5 ml/kg/h or 10% decline in lactate from baseline, reasonable components of a composite, because each is associated with short-term mortality of septic shock (5, 6). Intervention patients had NE started sooner (93 vs. 192 min), indicating that the intervention (early NE) was indeed tested. The primary endpoint was achieved in significantly more of the intervention than control group (76.1% vs. 48.4%); each component of the composite was achieved significantly earlier in the intervention group (i.e., the composite was not driven by one major component). There was a nominally lower mortality in the intervention than control group (15.5% vs. 21.9%; $P = 0.15$). This phase 2 RCT was not powered for mortality, but it is satisfying to see these short-term mortality results. There was no difference in the fluids administered, but the net fluid balance was not reported. One might have expected that early NE would lower net fluid balance (7). Interestingly, the intervention group had significantly fewer patients with cardiogenic pulmonary edema (14.4% vs. 27.7%) or new-onset arrhythmias (11% vs. 20%). The authors conclude that early low-dose NE was associated with earlier shock control.

This RCT fits a growing body of evidence that vasopressors should probably be started earlier. It aligns with a recent artificial intelligence (AI) study in which the AI clinician recommended more patients with sepsis should have been given vasopressors (17% vs. 30%) (8). Although we should not change practice on the basis of the study by Permpikul and colleagues (1), this trial and other work suggests that we should not delay starting vasopressors. If there is delay inserting a central venous catheter, then one should consider peripheral low-dose dilute NE temporarily rather than delay vasopressor(s). If clinicians delay starting vasopressor(s) because of a lack of critical care bed availability, then again, this RCT suggests they probably should not delay. Managing a patient on a general ward, without vasopressors, hoping that in time blood pressure will improve and thus not require critical care, may lead to worse outcomes for patients.

The investigators should be congratulated for conducting a high-quality trial, with an interesting design, incorporating a blinded placebo infusion in what is a challenging research area. The strengths of the study include computerized randomized controlled design, well-matched patients (although MAP was lower initially in the NE group), the composite primary endpoint, intention-to-treat primary analyses, and the method for organ dysfunction analyses (9). Remarkably, these investigators were able to identify, consent, and randomize patients within 1 hour of meeting inclusion criteria, which is fundamental in examining early treatment.

Limitations are that the effects of NE to increase MAP would have been apparent, and blinding was not 100% possible. Second, many (47%) trial patients not on dialysis or mechanical ventilation were transferred to medical wards for care, which may have increased the risks of protocol violations and adverse events.

The NE group achieved MAP and lactate clearance greater than 10% within 6 hours, and time to target urine output and lactate were lower. Thus, earlier NE may have improved general tissue and renal perfusion; the better urine output could be due to earlier MAP greater than 65 mm Hg and higher early renal perfusion pressure. However, this did not translate into less need for renal replacement therapy.

Early NE may be more effective than later NE because patients have less organ injury, and prevention of organ dysfunction is possible. Early NE may also allow lower doses of NE and so fewer adverse effects, and sustained elevation of NE down-regulates adrenergic receptors, which can further increase NE dose requirements (10) (Figure 1). Early low-dose NE could also beneficially modulate immunity in sepsis (11).

Although there are no clinical predictive biomarkers for response to NE, variants in the $\beta_2$-adrenergic receptor gene (12) associated with mortality of septic shock could be predictive biomarkers of response to NE.

What are the wider implications of the current RCT? The RCT by Permpikul and colleagues (1) is similar to prior RCTs of early vasopressin (13) versus NE, NE versus epinephrine (14), NE versus dopamine (15), and vasopressin versus NE in septic shock (16). These RCTs established that NE is superior to dopamine and equivalent to vasopressin and epinephrine. In VANISH (Vasopressin vs. Norepinephrine as Initial Therapy in Septic Shock) (13), early vasopressin was no different regarding mortality than standard care. There was no difference in overall mortality between vasopressin and NE in VASST (Vasopressin and Septic Shock Trial) (16), but vasopressin may have been more effective than NE in patients with less severe shock. A propensity-matched cohort study (17) showed that lower doses of vasopressin were associated with similar outcomes compared with



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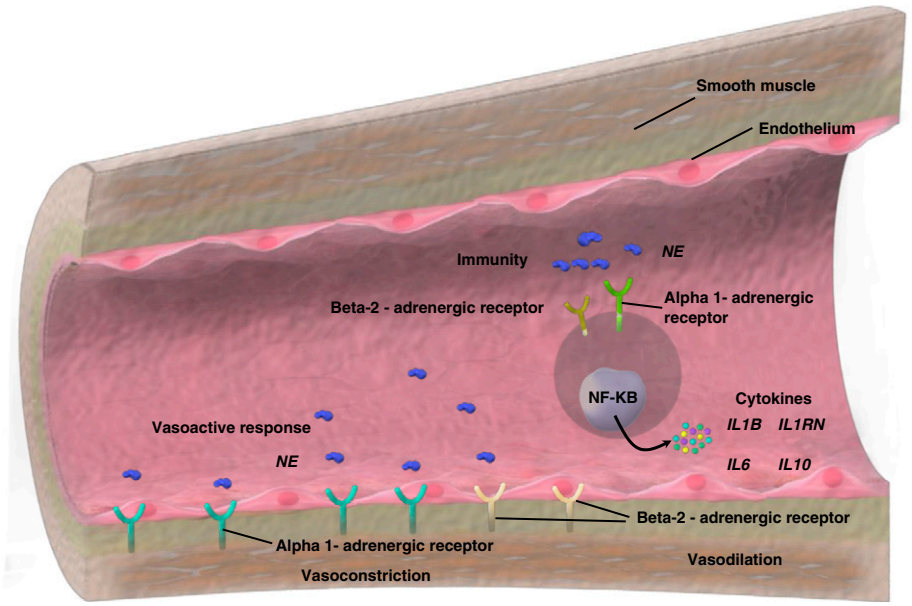


**Figure 1.** Norepinephrine (NE, blue) binds to $\alpha_1$-adrenergic receptors of vascular smooth muscle to induce vasoconstriction and binds to $\alpha_1$- and $\beta_2$-adrenergic receptors on leukocytes to differentially modulate immune response in sepsis. Exposure to NE also downregulates $\alpha_1$- and $\beta_2$-receptor density, which could alter sensitivity to NE, thereby leading to increased infusion doses of NE and greater risk of adverse vascular and immune effects. NF = nuclear factor.

NE. An RCT of early vasopressin and NE versus NE monotherapy found that patients who received early vasopressin and NE achieved MAP of 65 mm Hg faster than those receiving NE monotherapy (18).

Thus, NE remains the primary vasopressor in septic shock, but the existing evidence underlines the importance of early appropriate treatment in sepsis. The current RCT suggests that early low-dose NE may be superior to current standard care. We now need a large multicenter phase 3 RCT of early low-dose NE powered for mortality and organ dysfunction. ■

**Author disclosures** are available with the text of this article at www.atsjournals.org.

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# Sleep and Wakefulness Evaluation in Critically Ill Patients
## One Step Forward

Over the last two decades, there has been a growing interest in sleep abnormalities of critically ill patients. Early studies using standard EEG criteria (1) have shown that these patients exhibit a reduction in REM and N3 stages of sleep and excessive sleep fragmentation, whereas the normal circadian rhythm is lost (2, 3). Thus, although the total sleep time may be normal, the quality of sleep is poor, and these patients could be considered as sleep deprived (4, 5). Sleep disturbances remain mostly undiagnosed, mainly owing to a lack of easily applicable diagnostic tools.

Recent studies have shown that in critically ill patients, the conventional EEG criteria for evaluation of sleep and wakefulness are difficult to apply (6, 7). In these patients, the K complexes and sleep spindles, used to identify N2 stage, are often absent (atypical sleep), whereas EEG during behaviorally confirmed wakefulness may be abnormal, characterized by an increase in slow-wave activity and a decrease in high-frequency activity (pathological wakefulness). These EEG patterns have been observed in 30–50% of critically ill patients and usually coexist (6, 8). It is important to realize that EEG during pathological wakefulness may be similar to non-REM sleep, and therefore the diagnosis necessitates behavioral criteria. It follows that sleep assessment offline is unable to distinguish pathological wakefulness from sleep.

Recently, Younes and colleagues described and validated a continuous index, the odds ratio product (ORP), for the evaluation of sleep depth in ambulatory patients, using EEG power spectrum analysis (9). The ORP is an index of sleep depth derived from the relationship of powers of different EEG frequencies in 3-second epochs, and it ranges between 0 (very deep sleep) and 2.5 (full wakefulness). An ORP value less than 1.0 predicts sleep, and an ORP value greater than 2.0 wakefulness with 95% accuracy, whereas the range between 1.0 and 2.0 represents unstable sleep. An ORP value greater than 2.2 predicts wakefulness with almost 100% accuracy (9).

In this issue of the *Journal*, Dres and colleagues (pp. 1106–1115) report, for the first time, ORP in mechanically ventilated critically ill patients during a 15-hour period preceding a spontaneous breathing trial (SBT) (10). The aim was to investigate if ORP and polysomnographic indices indicating atypical sleep and pathological wakefulness are associated with SBT outcome. Among 44 eligible patients, 37 had an acceptable quality of EEG recordings and were included in the study. ORP analysis was possible in 31 of them (84%). During the total recording period, the average ORP, the percentages of total recording time with ORP greater than 1.5, greater than 2.0, and greater than 2.2, and intraclass correlation coefficient between ORP in the right and left hemispheres (R/L ORP) were calculated. In the general population, the latter index averages 0.87 (0.76–0.95; 10th–90th percentile range) and is rarely less than 0.7 during the night (M. Younes, M.D., Ph.D., written communication, February 3, 2019), indicating that sleep depth changes in parallel in both hemispheres. Nineteen patients (51%) successfully passed the SBT, whereas 18 (49%) failed. Among the success group, 11 were extubated, and 8 were considered unready for extubation for various reasons. Pathological wakefulness or atypical sleep was highly prevalent, occurring in 14 (38%) and 17 (46%) patients, respectively, whereas conventional scoring of sleep was feasible only in 19 patients (51%). Neither atypical sleep/pathological wakefulness nor sleep architecture was associated with SBT outcome.

These results contrast with those of Thille and colleagues (8), who observed that in difficult-to-wean patients, atypical sleep was associated with longer weaning time. The difference is likely due to the patients studied because Thille and colleagues studied



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ORIGINAL ARTICLE

# Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER)
## A Randomized Trial

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## Abstract

**Rationale:** Recent retrospective evidence suggests the efficacy of early norepinephrine administration during resuscitation; however, prospective data to support this assertion are scarce.

**Objectives:** To conduct a phase II trial evaluating the hypothesis that early low-dose norepinephrine in adults with sepsis with hypotension increases shock control by 6 hours compared with standard care.

**Methods:** This single-center, randomized, double-blind, placebo-controlled clinical trial was conducted at Siriraj Hospital, Bangkok, Thailand. The study enrolled 310 adults diagnosed with sepsis with hypotension. The patients were randomly divided into two groups: early norepinephrine ($n = 155$) and standard treatment ($n = 155$). The primary outcome was shock control rate (defined as achievement of mean arterial blood pressure ⩾65 mm Hg, with urine flow ⩾0.5 ml/kg/h for 2 consecutive hours, or decreased serum lactate ⩾10% from baseline) by 6 hours after diagnosis.

**Measurements and Main Results:** The patients in both groups were well matched in background characteristics and disease severity. Median time from emergency room arrival to norepinephrine administration was significantly shorter in the early norepinephrine group (93 vs. 192 min; $P < 0.001$). Shock control rate by 6 hours was significantly higher in the early norepinephrine group (118/155 [76.1%] vs. 75/155 [48.4%]; $P < 0.001$). The 28-day mortality was not different between groups: 24/155 (15.5%) in the early norepinephrine group versus 34/155 (21.9%) in the standard treatment group ($P = 0.15$). The early norepinephrine group was associated with lower incidences of cardiogenic pulmonary edema (22/155 [14.4%] vs. 43/155 [27.7%]; $P = 0.004$) and new-onset arrhythmia (17/155 [11%] vs. 31/155 [20%]; $P = 0.03$).

**Conclusions:** Early norepinephrine was significantly associated with increased shock control by 6 hours. Further studies are needed before this approach is introduced in clinical resuscitation practice.

Clinical trial registered with www.clinicaltrials.gov (NCT01945983) (CENSER trial).

**Keywords:** septic shock; norepinephrine; resuscitation; early norepinephrine administration; sepsis with hypotension

Septic shock is characterized by systemic vasodilatation and vascular leakage arising from systemic inflammation induced by serious infection (1). Management, besides specific treatments consisting of antibiotics and source removal, includes effective restoration of the hemodynamic derangement and effective organ support. Generally, intravenous fluid is given first, followed by infusion of vasopressors when the blood pressure goal is not achieved after reaching the optimal intravascular volume (2).

Recently, several studies advocated the benefits of administering norepinephrine at the beginning of resuscitation. A rat model of endotoxic shock (3) demonstrated that norepinephrine administration at the early stage of endotoxic shock improved mean

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## At a Glance Commentary

**Scientific Knowledge on the Subject:** Recent evidence from animal studies and retrospective human studies has indicated the efficacy of early norepinephrine administration during septic shock resuscitation. However, there was limited information from prospective randomization trials to support this postulation.

**What This Study Adds to the Field:** In this double-blind, randomized, controlled trial that enrolled 310 adults with sepsis with hypotension, early norepinephrine administration resulted in a significantly higher shock control rate than standard treatment (76.1% vs. 48.4%, respectively). The findings of this study support the benefit of early administration of norepinephrine at the initiation of sepsis with hypotension resuscitation, together with fluid therapy.

arterial pressure, aortic blood flow, and sustained mesenteric blood flow. In humans, a retrospective study on a patient cohort with early norepinephrine administration revealed a shorter time to blood pressure goal achievement and favorable mortality outcome (4). Another study demonstrated increased cardiac preload and cardiac output in patients with life-threatening hypotension who received early norepinephrine after fluid replacement (5). Finally, a cohort analysis of patients who underwent septic shock resuscitation showed a mortality advantage from early norepinephrine use and illustrated the effect of delayed use of this agent (6). Notably, all of these studies were retrospective, which means that they were all subject to unavoidable selection biases, such as hypotension severity, and fluid volume administered before norepinephrine initiation. Therefore, we performed a randomized controlled trial to examine the hypothesis that administering low-dose norepinephrine at the beginning of sepsis-induced hypotension resuscitation accelerates shock control. Some of the results of these studies have been previously reported in the form of an abstract (7).

## Methods

### Trial Design

This phase II, randomized, double-blind, placebo-controlled clinical trial was conducted at the Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand during the October 2013 to March 2017 study period. Siriraj Hospital is Thailand's largest university-based national tertiary referral center. The trial was funded by Siriraj Critical Care Research Funding, and the funder had no role in the study design, analysis, or outcome assessment. The study protocol was developed by the investigator committee and approved by the Siriraj Institutional Review Board (approval no. Si 507/2013). The study complied with all of the principles set forth in the Declaration of Helsinki (1964) and its subsequent provisions. Informed consent to participate was obtained from each patient, or their legal guardian if the participant was unable to provide consent, before inclusion in the study. All participant screening and enrollment was performed by the coinvestigators (Figure 1). The details of the screening and enrollment processes are available in the online supplement. The outcome evaluation, data management, and analysis were conducted by the principal investigator and a statistician, both of whom were blinded to the patient enrollment and treatment process.

### Participant Enrollment, Randomization, and Intervention Assignment

Adults aged 18 years or older who presented at the emergency room with hypotension determined by mean arterial blood pressure (mABP) lower than 65 mm Hg and infection as the suspected cause were eligible for enrollment if they met the diagnostic criteria for sepsis according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 (8). Patients who met the septic shock diagnostic criteria for more than 1 hour before randomization and those who had acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active cardiac arrhythmias, active gastrointestinal hemorrhage, pregnancy, seizure, drug overdose, burn injury, trauma, requirement for immediate surgery, or advanced-stage cancer were excluded. Patients who signed to refuse medical treatment, including fluid resuscitation, vasopressor, and endotracheal intubation, were also excluded.

After enrollment, patients were randomly assigned in a 1:1 ratio by their sequential number of enrollment to receive either early norepinephrine administration

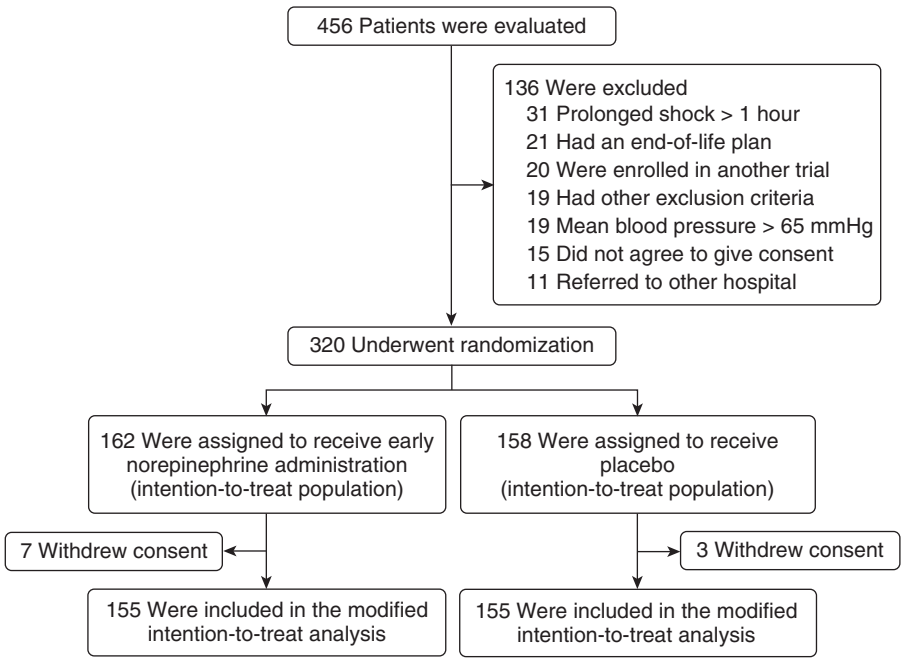



**Figure 1.** Flow diagram describing the screening, recruitment, and randomization of patients.

(early norepinephrine group) or placebo (standard treatment group), together with fluid resuscitation at the initiation of hypotension resuscitation. Randomization was performed using a computer-generated randomization table derived from www.randomization.com. This process was performed by an investigator (S.T.) who had no other role in patient enrollment or management. The other investigators, the patients, the patients' relatives, the attending physicians, and the nurses were all blinded to the study assignment. The study drug (norepinephrine or placebo) was prepared by a pharmacist, who had no other role in the trial. The study drugs were packaged in identically shaped containers labeled with sequential numbers according to the randomization table order. For the study drug, 4 mg of norepinephrine was mixed with 250 ml of 5% dextrose in water (5%D/W), giving a final norepinephrine concentration of 16 μg/ml. For the placebo comparator, 250 ml of 5%D/W was prepared. The study drug was infused via either peripheral line or central venous catheter (when available) at an individually adjusted rate according to the patient's body weight to achieve a dose of norepinephrine of 0.05 μg/kg/min. The study drug was infused for a period of 24 hours without titration in both groups.

All eligible patients received treatment for septic shock according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 (8). This included infusion of crystalloid solution, appropriate antibiotic therapy, source control, and organ support as directed by the attending physicians. The infusion rate and volume of intravenous fluid therapy was ordered according to the discretion of the treating clinician. If the hemodynamic goal (mABP $\geq$ 65 mm Hg) was not reached after optimal fluid (at least 30 ml/kg) and study drug infusion, open-label vasopressors were permitted when no attenuation of shock was observed.

After initial resuscitation in the emergency room, patients who required endotracheal intubation for mechanical ventilation, required initiation of renal replacement therapy, and/or required invasive hemodynamic monitoring were transferred to the medical ICU. Hemodynamically stable patients with no indications for mechanical ventilator or renal replacement therapy support were transferred to the general medical ward. The nurse to patient ratio was 1:1 in ICU and 1:3 in general medical ward. All patients admitted to the ICU had an arterial line inserted for continuous blood pressure monitoring.

### Outcome Assessment

The primary outcome of this study was shock control rate by 6 hours after diagnosis of sepsis with hypotension. Shock control rate was defined as achievement of sustained mABP of at least 65 mm Hg (9), together with evidence of adequate tissue perfusion. Patient's blood pressure was measured every 15 minutes after enrollment, either by automated noninvasive method or via an arterial line, when available. Target mABP achievement was defined as mABP of 65 mm Hg or higher, persisting for two consecutive measurements. Adequate tissue perfusion was defined as continuation of urine flow at more than 0.5 ml/kg/h for 2 consecutive hours, or decreased in serum lactate by more than 10% from the initial lactate level (10–12).

The secondary outcomes were 28-day mortality and hospital mortality. Rate of respiratory failure requiring mechanical ventilator support, rate of renal failure requiring renal replacement therapy, and number of organ support-free days to Day 28 were also recorded. The calculation of organ support-free days to Day 28 was based on the formula proposed by Russell and colleagues (13) (*see* the online supplement).

For safety outcome assessment, we recorded new onset of cardiac arrhythmia, organ ischemia, and cardiogenic or noncardiogenic pulmonary edema from diagnosis of sepsis with hypotension to hospital discharge or death. Causes of death were classified into refractory septic shock, sequelae of multiple organ failure, recurrent infection, sudden cardiac death unrelated to septic shock, and other causes. The definitions of all safety outcomes and causes of death are presented in the online supplement. The adjudication of safety outcomes and causes of death was performed by the attending physician according to the prespecified definitions. These assessments were performed prospectively on a day-by-day basis.

### Statistical Analysis

According to our previous study (12), the sample size calculation was based on a predicted rate of shock control by 6 hours after sepsis with hypotension resuscitation of 60% in the standard treatment group versus 80% in the early norepinephrine group. Enrollment of 150 participants per group would provide at least 80% power to assess the difference in the primary outcome between the two groups at a two-sided alpha error of 0.05. All primary and secondary outcomes analyses were based on the intention-to-treat principle. Patients who died before primary outcome assessment were considered treatment failure.

We used the Wilcoxon rank sum test for continuous variables and the chi-square test or Fisher exact test, where appropriate, for categorical variables. The primary outcome and safety outcomes were evaluated by the chi-square test. For the 28-day mortality analysis, time to death was calculated from date of septic diagnosis to date of death. Survival distributions in the two groups were estimated by plotting Kaplan-Meier curves. The hazard ratio of 28-day mortality was calculated by the Cox proportional hazards model. Values of $P$ less than 0.05 were considered to indicate statistical significance. All data analyses were performed using SPSS Statistics version 18 (SPSS Inc.).

## Results

### Patients

A total of 456 patients with an mABP lower than 65 mm Hg were screened. Of those, 320 patients satisfied the inclusion criteria and were randomized into either the early norepinephrine group or the standard treatment group. Seven patients in the study group and three patients in the control group later withdrew their consent to participate. Of the remaining 310 patients, 155 patients were randomly allocated to each of the two groups (Figure 1). Patients' baseline characteristics, including age, underlying conditions, and disease severity, were well matched between groups. The following median baseline values indicate the severity of the study participants: Acute Physiology and Chronic Health Evaluation II score of 20 (interquartile range [IQR], 16–26), mABP of 56 mm Hg (IQR, 51–60), and serum lactate level of 2.8 mmol/L (IQR, 1.8–5.3) (Table 1). No patients in either group required mechanical ventilator or renal replacement therapy before randomization.

There was no significant difference in median time from diagnosis to study drug

**Table 1.** Patients' Baseline Characteristics*

| Characteristics | Early Norepinephrine (*n* = 155) | Standard Treatment (*n* = 155) |
|---|---|---|
| Age, median (IQR), yr | 65 (54–76) | 68 (55–77) |
| Male sex, *n* (%) | 71 (45.8) | 77 (49.7) |
| Body mass index, median (IQR), kg/m$^2$ | 21.6 (19.6–23.8) | 22.1 (19.4–24.3) |
| APACHE II score, median (IQR)† | 21 (15–26) | 20 (16–26) |
| Time from emergency room arrival to diagnosis, median (IQR), min | 23 (5–168) | 25 (10–185) |
| Comorbidities, *n* (%) | | |
| Hypertension | 77 (49.7) | 85 (54.8) |
| Diabetes mellitus | 51 (32.9) | 53 (34.2) |
| Malignancy | 41 (26.5) | 41 (26.5) |
| Immunosuppression | 38 (24.5) | 34 (21.9) |
| Chronic kidney disease | 27 (17.4) | 37 (23.9) |
| Coronary artery disease | 25 (16.1) | 28 (16.8) |
| Stroke | 19 (12.3) | 15 (9.7) |
| Cirrhosis | 14 (9) | 13 (8.4) |
| Source of infection, *n* (%) | | |
| Urinary tract infection | 47 (30.3) | 45 (29) |
| Pneumonia | 40 (25.8) | 37 (23.9) |
| Intraabdominal infection | 31 (20) | 33 (21.3) |
| Skin and soft tissue infection | 15 (9.7) | 12 (7.7) |
| Others | 12 (7.7) | 14 (9) |
| Unable to identify source of infection | 10 (6.5) | 14 (9) |
| Hemoculture positive for organism | 25 (16.1) | 27 (17.4) |
| Identified pathogens, *n* (%)‡ | | |
| Gram-positive cocci | 20 (12.7) | 21 (13.5) |
| Gram-negative bacilli | 87 (56.1) | 73 (47.1) |
| Fungus | 2 (1.3) | 4 (2.6) |
| Virus | 3 (1.9) | 6 (3.9) |
| Unable to identify pathogen | 39 (26.2) | 51 (33.1) |
| Physiologic variables, median (IQR) | | |
| Temperature, ˚C | 38.0 (36.8–38.9) | 38.1 (36.8–39.0) |
| Initial mean arterial pressure, mm Hg | 56 (50–59) | 57 (52–62) |
| Initial heart rate, beats/min | 110 (90–128) | 108 (86–122) |
| Initial respiratory rate, breaths/min | 24 (22–30) | 24 (24–32) |
| White cell count, cells/mm$^3$ | 11,990 (7,070–19,890) | 13,690 (6,480–19,630) |
| Platelet count, platelets/mm$^3$ | 169,000 (85,000–266,000) | 157,000 (79,000–251,000) |
| Lactate, mmol/L | 3.0 (1.8–5.7) | 2.7 (1.8–4.8) |
| Lactate >2 mmol/L, *n*/total *n* (%) | 106/155 (68.3) | 102/155 (65.8) |

*Definition of abbreviations*: APACHE = Acute Physiology and Chronic Health Evaluation; IQR = interquartile range.
*There were no significant differences between the two groups in baseline characteristics, excepted for initial mean arterial pressure, which was lower in the early norepinephrine administration group ($P = 0.02$).
†The APACHE II score, a severity-determining score, ranges from 0 to 71. Higher scores indicate more severe disease.
‡Data of identified pathogens were missing for four patients in the early norepinephrine group.

initiation, or time from diagnosis to open-label norepinephrine initiation between early norepinephrine and standard treatment groups. Median time from emergency room arrival to norepinephrine administration was significantly shorter in the early norepinephrine group than in the standard treatment group (93 min [IQR, 72–114] vs. 192 min [IQR, 150–298]; $P < 0.001$) (Table 2). The proportion of patients that was admitted to the ICU was not different between groups (54.8% in the early norepinephrine group vs. 51.6% in the standard treatment group; $P = 0.57$). Among patients who were admitted to the ICU, the median time from diagnosis to ICU admission was similar between the study group and the control group (6 h and 36 min [IQR, 4:35–9:52] vs. 6 h and 35 min [IQR, 5:15–10:34]; $P = 0.34$). Among those who were transferred to the general medical ward, median time from diagnosis to admission was also not significantly different between the early norepinephrine group and the standard treatment group (6 h and 23 min [IQR, 4:25–10:34] vs. 6 h and 45 min [IQR, 4:24–10:54]; $P = 0.66$) (Table 2).

### Outcomes

The shock control rate by 6 hours after the initiation of resuscitation was higher in the early norepinephrine group than in the standard treatment group (76.1% vs. 48.4%; odds ratio, 3.4; 95% confidence interval [CI], 2.09–5.53; $P < 0.001$) (Table 3). For the individual endpoints by 6 hours, the achievement of target mABP (>65 mm Hg), urine output (>0.5 ml/kg), and lactate clearance (>10%) were all significantly higher in the early norepinephrine group (all $P < 0.05$). However, the rate of lactate normalization was not different between groups. There were more patients in the early norepinephrine group who achieved all targets by 6 hours than patients in the standard treatment group (31.0% vs. 17.4%; $P = 0.005$). Similarly, there were more

**Table 2.** Treatments Administered

| Data on Hemodynamic Management and Organ Support | Early Norepinephrine (*n* = 155) | Standard Treatment (*n* = 155) | *P* Value |
|---|---|---|---|
| Time from diagnosis to study drug initiation, median (IQR), h:min | 1:10 (0:50–1:30) | 1:10 (0:45–1:40) | 0.66 |
| Time from diagnosis to open-label norepinephrine initiation, median (IQR), h:min | 3:00 (2:12–4:30) | 2:47 (2:05–4:33) | 0.38 |
| Time from diagnosis to any norepinephrine initiation, median (IQR), h:min | 1:10 (0:50–1:30) | 2:47 (2:05–4:33) | <0.001 |
| Time from emergency room arrival to administration of any norepinephrine, median (IQR), h:min | 1:33 (1:12–1:54) | 3:12 (2:30–4:58) | <0.001 |
| Vasopressors (open label) | | | |
| Norepinephrine, *n* (%) | 105 (67.7) | 124 (80) | 0.014 |
| Maximum dose, median (IQR), μg/kg/min* | 0.1 (0.05–0.18) | 0.1 (0.05–0.15) | 0.59 |
| Epinephrine, *n* (%) | 27 (17.4) | 31 (20) | 0.56 |
| Maximum dose, median (IQR), μg/kg/min* | 0.41 (0.28–1.2) | 0.4 (0.26–0.60) | 0.41 |
| Dopamine, *n* (%) | 6 (3.9) | 3 (1.3) | 0.31 |
| Maximum dose, median (IQR), μg/kg/min* | 10.3 (4.7–14.7) | 6.7 (4.9–7.2) | 0.31 |
| Dobutamine, *n* (%) | 5 (3.2) | 5 (3.2) | 1.0 |
| Maximum dose, median (IQR), μg/kg/min* | 4.7 (2.4–6.7) | 3.8 (3.3–4.3) | 0.69 |
| Fluid administered | | | |
| Fluid administered before study drug initiation, median (IQR), ml | 800 (600–1,000) | 800 (500–1,000) | 0.34 |
| Fluid administered before open-label norepinephrine initiation, median (IQR), ml | 2,080 (1,400–2,600) | 1,900 (1,345–2,278) | 0.32 |
| Fluid administered before open-label norepinephrine initiation, median (IQR), ml/kg | 32.3 (24.5–45.9) | 29.8 (21.8–40.9) | 0.3 |
| Fluid administered in first 1 h, median (IQR), ml | 800 (600–1,000) | 800 (600–1,000) | 0.64 |
| Fluid administered in 0–6 h, median (IQR), ml | 2,450 (1,914–3,200) | 2,600 (2,154–3,240) | 0.33 |
| Fluid administered in Day 1, median (IQR), ml | 5,032 (3,950–6,060) | 5,025 (3,855–5,853) | 0.66 |
| Fluid administered in Day 2, median (IQR), ml | 1,825 (964–2,575) | 1,680 (987–2,275) | 0.28 |
| Fluid administered in Day 3, median (IQR), ml | 845 (185–1,733) | 1,000 (120–1,755) | 0.87 |
| Central venous catheter insertion, *n* (%) | 67 (43.8) | 71 (46.1) | 0.68 |
| Time from diagnosis to central venous catheter insertion, median (IQR), h:min, (*n* = 138) | 4:10 (2:45–8:30) | 4:00 (2:30–6:40) | 0.64 |
| Initial central venous pressure, median (IQR), mm Hg, (*n* = 138) | 8 (5–14) | 9 (7–12) | 0.41 |
| ICU admission, *n* (%) | 85 (54.8) | 80 (51.6) | 0.57 |
| Time from diagnosis to ICU admission, median (IQR), h:min, (*n* = 165) | 6:36 (4:35–9:52) | 6:35 (5:15–10:30) | 0.34 |
| Time from diagnosis to general medical ward admission, median (IQR), h:min, (*n* = 145) | 6:23 (4:25–10:34) | 6:45 (4:24–10:54) | 0.66 |
| ICU length of stay, median (IQR), d, (*n* = 165) | 2 (0–6) | 1 (0–5) | 0.57 |
| Hospital length of stay, median (IQR), d, (*n* = 310) | 10 (6–21) | 10 (7–17) | 0.37 |

*Definition of abbreviation*: IQR = interquartile range.
*The median and IQR of vasopressor doses are derived from the patients who received a dose more than zero.

patients in the study group than in the control group who achieved both target mABP and target urine output (35.5% vs. 24.5%; $P = 0.04$). In contrast, achievement of both target mABP and target lactate clearance greater than 10% within 6 hours was not different between the study and control groups (9.7% vs. 6.5%; $P = 0.3$) (Table 3).

Median time from diagnosis to achieving target mABP greater than or equal to 65 mm Hg was shorter in the early norepinephrine group (3:30 h vs. 4:45 h; $P < 0.001$). The median time from diagnosis to achieving shock control was 4 hours 45 minutes in the study group, which was significantly shorter than the 6 hours 2 minutes in the control group ($P < 0.001$). Median of mABP was significantly higher in the early norepinephrine group during the fourth to sixth hour after diagnosis ($P < 0.05$) (*see* Figure E3A in the online supplement).

Regarding the amount of intravenous fluid, there was no significant difference between groups for the total volume of fluid administered at any time. Open-label norepinephrine was used in 67.7% of study group patients, compared with 80% of control group patients ($P = 0.01$). Although patients in the early norepinephrine group received a higher median norepinephrine dosage during the second to fifth hours after diagnosis, the norepinephrine dosage was the same between groups after the sixth hour (*see* Figure E3B). Other vasoactive agents, including epinephrine, dopamine, and dobutamine, were used in similar proportions when compared between groups. No patient in either group had cessation of study medication because of high blood pressure.

Mortality at 28 days was 15.5% in the early norepinephrine group and 21.9% in the standard treatment group (relative risk, 0.79; 95% CI, 0.53–1.11; $P = 0.15$) (Table 3). The Kaplan-Meier curves of 28-day mortality are shown in Figure 2. There was no difference between groups for the rates of mechanical ventilator support or renal replacement

**Table 3.** Clinical Outcomes

| Outcome | Early Norepinephrine (*n* = 155) | Standard Treatment (*n* = 155) | Odds Ratio or Relative Risk (95% CI)* | *P* Value |
|---|---|---|---|---|
| Primary outcome, *n* (%) | | | | |
| Achieved target mABP + tissue perfusion goal by 6 h | 118 (76.1) | 75 (48.4) | 3.4 (2.09–5.53) | <0.001 |
| Achieved target mABP + urine output + lactate clearance >10% by 6 h | 48 (31.0) | 27 (17.4) | 2.13 (1.24–3.64) | 0.005 |
| Achieved target mABP + urine output by 6 h | 55 (35.5) | 38 (24.5) | 1.69 (1.04–2.77) | 0.04 |
| Achieved target mABP + lactate clearance >10% by 6 h | 15 (9.7) | 10 (6.5) | 1.55 (0.68–3.57) | 0.3 |
| Secondary outcomes | | | | |
| Mortality at 28 d, *n* (%) | 24 (15.5) | 34 (21.9) | 0.79 (0.53–1.11) | 0.15 |
| Hospital mortality, *n* (%) | 35 (22.6) | 38 (24.5) | 0.95 (0.72–1.24) | 0.69 |
| Time from initial treatment to achieving target mABP + tissue perfusion goal, median (IQR), h:min | 4:45 (3:30–5:56) | 6:02 (4:20–9:18) | | <0.001 |
| Achieved target mABP by 6 h, *n* (%) | 134 (86.5) | 104 (67.1) | 3.13 (1.77–5.53) | <0.001 |
| Mean arterial pressure at 6 h, median (IQR), mm Hg | 74 (69–79) | 72 (66–78) | | 0.22 |
| Time from initial treatment to achieving target mABP ⩾65 mm Hg, median (IQR), h:min | 3:30 (2:09–5:00) | 4:45 (3:15–7:00) | | <0.001 |
| Achieved target urine output within 6 h, *n* (%) | 107 (69) | 75 (48.4) | 2.47 (1.55–3.95) | <0.001 |
| Achieved target urine output by 0–2 h, *n* (%) | 13 (8.4) | 12 (7.7) | 1.09 (0.48–2.47) | 0.84 |
| Time from initial treatment to achieving target urine output, median (IQR), h:min | 4:30 (3:00–5:52) | 5:10 (4:00–9:37) | | 0.003 |
| Achieved target lactate clearance >10% by 6 h, *n* (%) | 64 (41.3) | 43 (27.7) | 1.87 (1.16–3.02) | 0.009 |
| Lactate level <2 mmol/L by 6 h | 73 (47.1) | 62 (40.3) | 1.32 (0.84–2.07) | 0.23 |
| Time from initial treatment to achieving target lactate <2 mmol/L, median (IQR), h:min | 6:00 (3:57–15:12) | 8:45 (5:10–13:45) | | 0.003 |
| Days alive and free of vasopressors to Day 28, median (IQR), d† | 26 (23–27) | 25 (7–27) | | 0.35 |
| Mechanical ventilator support, *n* (%) | 58 (37.4) | 59 (38.1) | 0.99 (0.79–1.24) | 0.91 |
| Days alive and free of mechanical ventilator to Day 28, median (IQR), d† | 28 (14–28) | 28 (7–28) | | 0.42 |
| Renal replacement therapy, *n* (%) | 19 (12.3) | 23 (14.8) | 0.89 (0.67–1.22) | 0.51 |
| Days alive and free of renal replacement therapy to Day 28, median (IQR), d† | 28 (20–28) | 28 (20–28) | | 0.7 |
| Days alive and free of organs support to Day 28, median (IQR), d† | 25 (0–27) | 25 (0–26) | | 0.23 |

*Definition of abbreviations*: CI = confidence interval; IQR = interquartile range; mABP = mean arterial blood pressure.
*Primary outcomes are given as odds ratios, and secondary outcomes are given as relative risk.
†Days alive and free of vasopressors, mechanical ventilator, renal replacement therapy, and organs support to Day 28 were calculated based on method previously described in Reference 13.

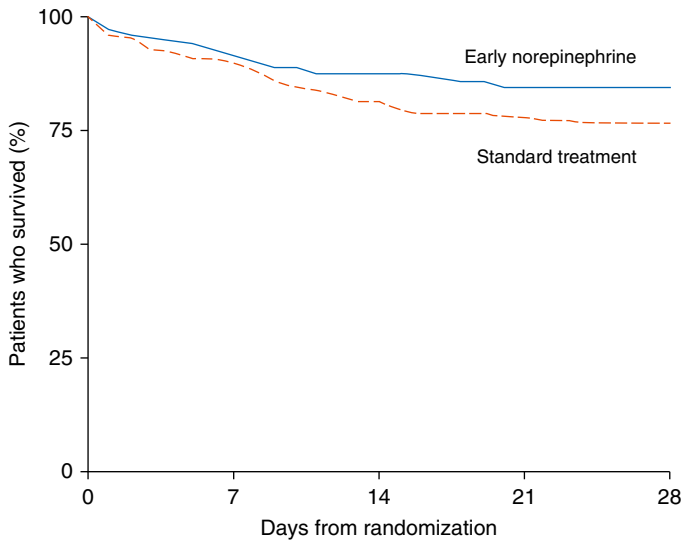
therapy (Table 3). The median number of organ support–free days to Day 28 also did not differ between the two groups.

Patients in the early norepinephrine group had a lower rate of cardiogenic pulmonary edema (14.4% vs. 27.7%; $P = 0.004$) and new-onset arrhythmia (11% vs. 20%; $P = 0.03$). However, other complications, including limb ischemia and intestinal ischemia, were similar between groups (Table 4). The leading cause of death was sequelae of multiple organ system failure, followed by refractory septic shock.

## Discussion

This double-blind randomized controlled trial revealed norepinephrine administration at the beginning of sepsis with hypotension resuscitation to be associated with a higher shock control rate by 6 hours compared with the standard treatment. Occurrence of organ failure, such as respiratory failure requiring ventilator support and renal failure requiring renal replacement therapy, did not differ between groups. However, two adverse events, cardiogenic pulmonary edema and new-onset arrhythmia, occurred in lower proportions in the early norepinephrine group.

This is the first study to assess the benefit of early norepinephrine administration for sepsis-related hypotension resuscitation on surrogate short-term, shock control endpoints. Early norepinephrine administration improved mABP, urine output, and lactate clearance by 6 hours. Our selected hemodynamic endpoints represent both macrocirculation




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Early Norepinephrine | 155 | 142 | 136 | 131 | 131 |
| Placebo | 155 | 139 | 126 | 121 | 119 |

**Figure 2.** Kaplan-Meier analysis of 28-day survival. The hazard ratio for death in the early norepinephrine group compared with the standard treatment group was 0.69 (95% confidence interval, 0.41–1.16; $P = 0.16$).

and microcirculation restoration. A target mABP of greater than or equal to 65 mm Hg was selected to represent macrocirculation restoration, because a previous study reported that the targeted mABP higher than 65 mm Hg did not improve mortality (9). Data from a recent multicenter retrospective analysis showed that patients with sepsis who had an mABP during ICU admission lower than 65 mm Hg, had a significantly higher risk of mortality, acute kidney injury, and myocardial injury (14).

For tissue perfusion evaluation, we used urine flow greater than 0.5 ml/kg/h for 2 consecutive hours as evidence of adequate kidney blood flow and splanchnic circulation restoration. In those who had no urine or urine flow less than 0.5 ml/kg/h, lactate clearance greater than 10% was used as the evaluative parameter. That evaluation protocol was based on evidence from a previous randomized controlled trial that found that shock resuscitation guided by serum lactate reduction associated with lower hospital mortality than those who did not monitor lactate clearance (15). From our previous report, the achievement of macrocirculation and microcirculation targets was associated with lower hospital mortality than the rate observed in patients who met only mABP target or no target at all (12).

As noted from the disease pathophysiology, vasodilatation and leakage are prominent features. Thus, effective restoration of the perfusion deficit should begin with both fluid repletion and vasopressors. Several retrospective studies in patients with septic shock support this hypothesis (4, 6). Specifically, shorter hypotension duration and lower mortality were noted in patients with early norepinephrine administration. The results of our study, which is the first randomized controlled trial to investigate the effect of early norepinephrine, revealed a shorter shock interval in the early norepinephrine group than in the standard treatment group.

The lower occurrences of congestive heart failure and new-onset arrhythmia in the early norepinephrine group were not observed in other studies. A study in coronary blood flow during sepsis revealed increased perfusion together with increased oxygen demand (16). Norepinephrine restored global perfusion, but did not further increase coronary blood flow. In an observational study, patients with septic shock and severe hypotension were given norepinephrine after median fluid resuscitation of 1,000 ml. Using a noninvasive measurement (PiCCOplus),

**Table 4.** Adverse Events and Causes of In-Hospital Death

| Events | Early Norepinephrine (*n* = 155) | Standard Treatment (*n* = 155) | Relative Risk (95% CI) | *P* Value |
|---|---|---|---|---|
| Adverse events, *n* (%) | | | | |
| Cardiogenic pulmonary edema | 22 (14.4) | 43 (27.7) | 0.70 (0.56–0.87) | 0.004 |
| Acute respiratory distress syndrome | 17 (11) | 14 (9) | 1.12 (0.75–1.68) | 0.56 |
| New-onset cardiac arrhythmia | 17 (11) | 31 (20) | 0.74 (0.56–0.94) | 0.03 |
| Hospital-acquired infection | 22 (14.5) | 21 (13.7) | 1.03 (0.74–1.43) | 0.85 |
| Upper gastrointestinal hemorrhage | 6 (3.9) | 5 (3.2) | 1.12 (0.58–2.15) | 0.73 |
| Acute limb and/or intestinal ischemia | 5 (3.2) | 3 (1.9) | 1.35 (0.55–3.32) | 0.47 |
| Skin necrosis | 1 (0.6) | 1 (0.6) | 1.0 (0.25–4.02) | 1.0 |
| Causes of in-hospital death, *n* (%) | | | | |
| Sequelae of multiple organ system failure | 18 (11.6) | 22 (14.2) | 0.9 (0.66–1.22) | 0.5 |
| Refractory septic shock | 4 (2.6) | 6 (3.9) | 0.83 (0.49–1.39) | 0.52 |
| Recurrent infection | 6 (3.9) | 4 (2.6) | 1.26 (0.58–2.71) | 0.75 |
| Sudden cardiac death unrelated to septic shock | 5 (3.2) | 3 (1.9) | 1.34 (0.55–3.31) | 0.72 |
| Other causes | 2 (1.3) | 3 (1.9) | 0.83 (0.40–1.72) | 0.66 |

*Definition of abbreviation*: CI = confidence interval.

improved cardiac output was noted by the mechanism of increasing cardiac preload and cardiac contractility (17). Thus, the lower cardiac events in our patients may be explained by decreasing oxygen demand resulting from shorter shock duration and improved cardiac contractility arising from early use of norepinephrine. However, the safety of early norepinephrine administration relative to lower incidence of congestive heart failure and new-onset arrhythmia still needs to be confirmed.

Splanchnic hypoperfusion is an important concern when norepinephrine is given early. Vasoconstriction induced by norepinephrine may aggravate internal organ ischemia and lead to patient deterioration (18, 19). Recent studies examined this concern and revealed that norepinephrine did not alter perfusion to the gut and kidney (20, 21). Although no objective measurements were made in the present study, there was no difference in prevalence of organ failure between groups. Our study revealed similar rates of acute limb ischemia, intestinal ischemia, and gastrointestinal bleeding between groups, which may indicate prolonged inadequate tissue perfusion during septic shock resuscitation.

Fluid overload is a common complication during sepsis resuscitation. Systemic inflammation causes intravascular fluid leakage into the interstitial area, and subsequent large amounts of crystalloid resuscitation can fill up both intravascular and interstitial spaces, resulting in total body fluid excess. Early use of norepinephrine decreases the use of fluid replacement, possibly by constricting the dilated vascular bed, and shortens resuscitation duration. This was described in the previously mentioned and another recently reported animal studies (3, 22) but not in our study. Possible explanations are that the study was performed during 2013–2017 when the Surviving Sepsis Campaign Guidelines were used, meaning that fluid was given toward a target intravascular volume or central venous pressure; and norepinephrine was used at a low dose (0.05 μg/kg/min) to avoid excessive vasoconstriction, a serious complication of norepinephrine, especially during inadequate preload, and this may result in suboptimal increased cardiac preload and vasoconstriction that was sufficient to reduce hypoperfusion duration, but not resuscitation volume.

Concerning the timing of intervention, our study showed a remarkably shorter duration from emergency room presentation to study drug initiation than previous septic shock management studies. The reported median time from emergency room presentation to randomization in the ProCESS, ARISE, and PROMISE trials was 162 minutes among the early goal-directed therapy groups and 159 minutes among the standard treatment group (23). In contrast, our median time from emergency room arrival to administration of the study drug was 93 minutes. Hence, patients in early norepinephrine group received norepinephrine at least 1 hour earlier than the patients in the previously mentioned trials.

This study has some limitations. First, we could not mask the effect of norepinephrine in the early norepinephrine group. The rapid increase in patient blood pressure may have provided clues to attending physicians. However, up to 20% of patients in the standard treatment group responded similarly to the placebo infusion. Second, because of the limited number of ICU beds available at our center, we had to transfer about 47% of patients that did not require mechanical ventilator or dialysis to the general medical ward. Moreover, some patients required adjustment of their norepinephrine infusion dosage and the use of vasopressors on the ward would be unlikely to occur at many institutions worldwide.

Third, this study did not aim to evaluate mortality, so the effect of early norepinephrine administration on mortality cannot be inferred from the results of this study. Furthermore, we did not control the resuscitation fluid rate, which resulted in variation among patients. This may have affected the treatment outcome. Lastly, this is a single-center trial, which could limit the generalizability of these findings to other care settings. Physician who decide to apply the results of this study to their routine clinical practice should carefully evaluate the context of this study and compare it with their own situation and setting. A multicenter trial with a larger population size, control of the rate of fluid resuscitation, and the timing of norepinephrine initiation is certainly required to assess the survival benefit of early norepinephrine as an intervention.

In conclusion, the results of this phase II clinical trial demonstrated significant association between early norepinephrine and increased shock control by 6 hours. Further studies are needed to confirm these findings before this approach can be introduced in clinical resuscitation practice. Future study should investigate the effect of early norepinephrine on organ dysfunction and mortality. ■

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**Figure 3**. Mean arterial pressure (Figure 3A.) and summation of study and open label norepinephrine (Figure 3B.) over time.

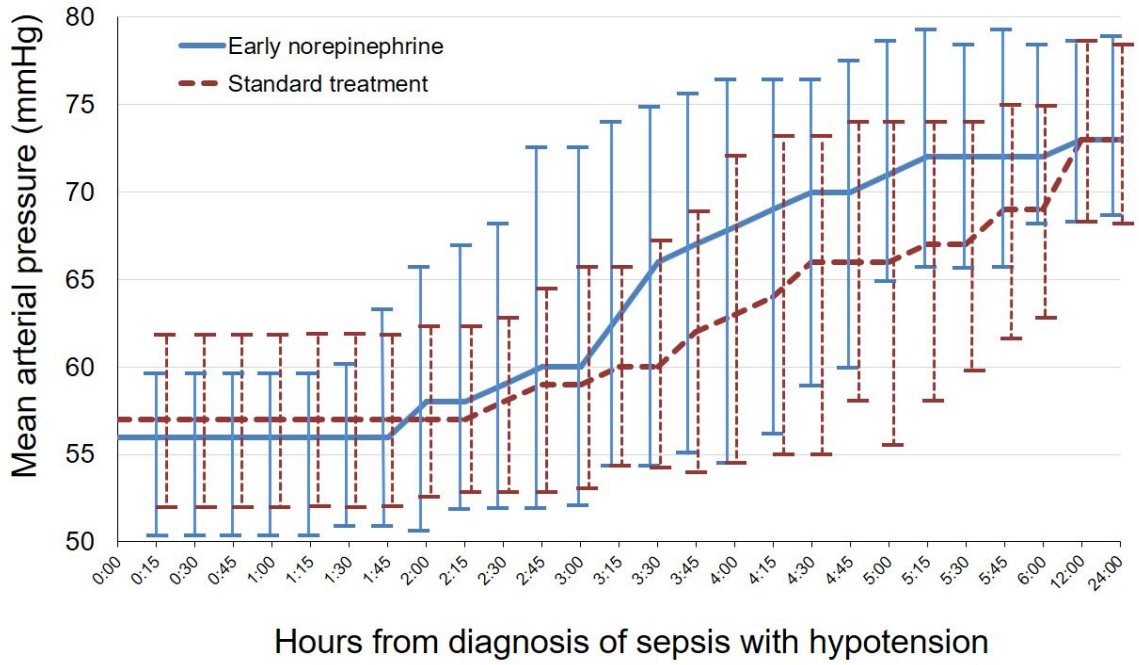


**Figure 3A**. Demonstrates median of mean arterial pressure and interquartile range (indicated by I bar) in the early norepinephrine group (blue line) and the standard treatment group (red doted line). Mean arterial pressure was significantly higher in the early norepinephrine group than in the standard treatment group during 3:30 to 6:00 hours diagnosis of sepsis with hypotension. ($P < 0.05$)

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**Figure 3**. Mean arterial pressure (Figure 3A.) and summation of study and open label norepinephrine (Figure 3B.) over time.

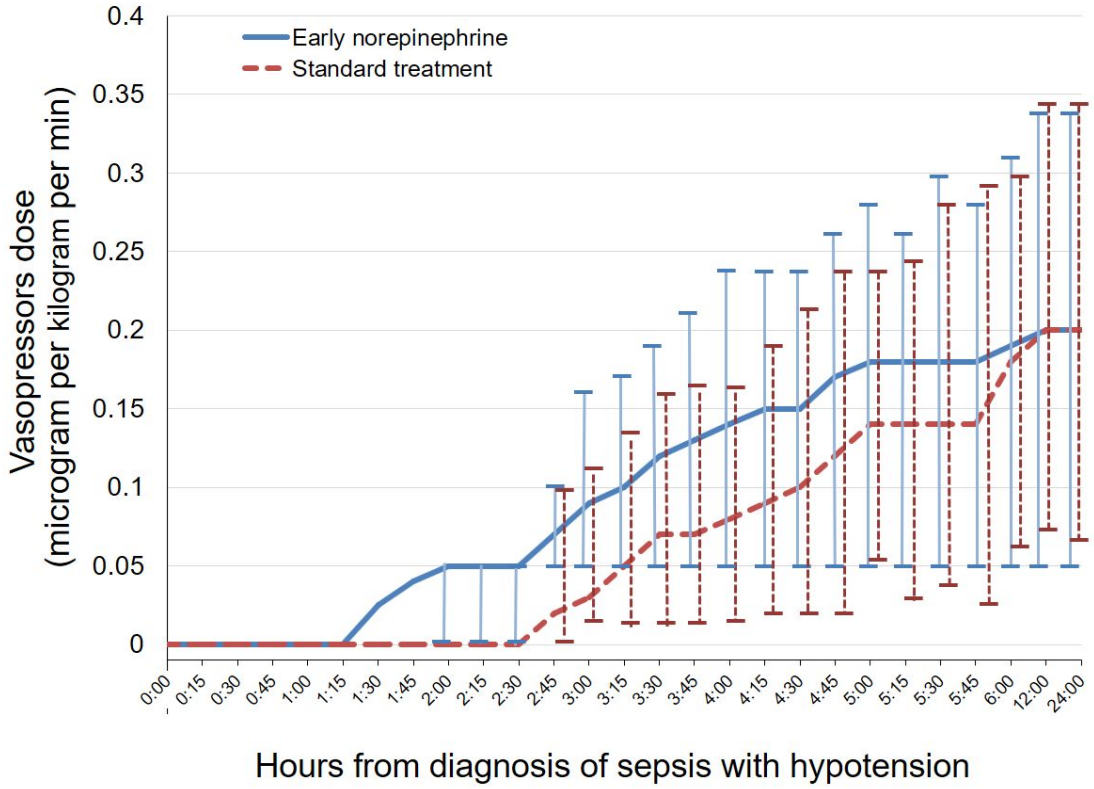


**Figure 3B**. Demonstrates median of summation of norepinephrine dose (study drug + open label norepinephrine) and interquartile range (indicated by I bar) in the early norepinephrine group (blue line) and the standard treatment group (red doted line). Patients in the early norepinephrine group received a significantly higher dose of norepinephrine than patients in the standard treatment group during 2:00 to 5:45 hours after diagnosis of sepsis with hypotension. (P <0.05)

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# Early Use of Norepinephrine for Sepsis: Promising Results That Require Confirmation

*To the Editor*:

Permpikul and colleagues demonstrated in a randomized controlled study that norepinephrine initiated early in the management of sepsis with arterial hypotension increased the rate of shock control at 6 hours (1). This result has potentially clinically significant consequences because it could alter the management of resuscitation in patients with sepsis and septic shock. However, some points regarding catecholamine use in this study should be noted.

First, it could be highlighted that epinephrine dose is more important than expected according to the 2012 and 2016 Surviving Sepsis Campaign guidelines (2, 3): 20% of patients in the placebo group were treated with epinephrine and 17.4% in the norepinephrine group. In contrast, De Backer and colleagues reported a maximum of 1.5% of patients with shock (mainly from septic origin) treated with open-label epinephrine (4). Prescription of epinephrine is most often limited to arterial hypotension that is refractory to high doses of norepinephrine (2, 3). However, in the present study, the maximum doses of norepinephrine prescribed do not seem to justify epinephrine initiation, as the 75% interquartile range in the control group was 0.15 μg/kg/min. In contrast, in the HYPRESS (Hydrocortisone for Prevention of Septic Shock) study (5), which included patients with sepsis, the average dose of norepinephrine in the control group was $0.4 \pm 0.8$ μg/kg/min.

Second, open-label norepinephrine was started in the placebo group 2.5 hours after inclusion, i.e., after 30 ml/kg of fluid expansion. At this time point, mean arterial pressure was, as expected, lower in the placebo group than in the norepinephrine group. However, despite this difference in mean arterial pressure, in Figure E3B in the online supplement of Reference 1, the slopes (representing the amount of norepinephrine per kilogram) are parallels between 2.5 and 5.75 hours, despite a persistent lower mean arterial pressure in the placebo group. Logically, a substantial steepening of the slope was expected in order to more quickly reach a mean arterial pressure above 65 mm Hg. This could suggest a vasopressor under resuscitation in the control group.

Third, it should be also be acknowledged that the case mix in this study, which had a high proportion of urinary tract infections, cannot be compared with European or North American case mixes in which pneumonias were most often predominant (5). Similarly, in the present study, the nurse-to-patient ratio was 1:3 in the ward, whereas in some countries, this ratio is applied in ICUs.

Finally, the results of the present study are promising but need to be confirmed in multicenter trials. ■

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## Norepinephrine for Early Shock Control in Sepsis

*To the Editor*:

Permpikul and colleagues recently conducted a phase 2 randomized trial of early low-dose norepinephrine in septic shock, published in the May 1 issue of the *Journal* (1). This trial should be lauded for its elegant design and for the difficulty of studying this topic. We would like to offer the following points of emphasis regarding other interesting findings in the trial, as well as data that support the need for further trials.

In the trial, patients were randomized to either placebo or fixed-dose norepinephrine in addition to open-label vasopressors. The intervention arm had a significantly faster time to shock control as defined by the authors. In the online supplement of Reference 1, there are two figures that we believe merit additional mention. Figures E3A and E3B imply that the average dose of norepinephrine required to achieve a mean arterial pressure (MAP) >65 mm Hg in both the study and control groups was around 0.1 μg/kg/min. This apparent threshold dose is also roughly twice that of the study drug and is suggestive of what should be a reasonable starting point for both future studies and potentially current clinical practice. These supplemental figures suggest that the intervention of early norepinephrine benefited most of the patients by providing a head start to the subsequent titration of open-label vasopressor. This is consistent with the significant proportion of the study group that ultimately required open-label vasopressors to achieve MAP control. Although these data require verification in other populations, they have interesting implications for future practice guidelines and clinical investigations.

Another finding from the study worth highlighting is the effect of protocols on the extremes of patient care. Although the reduction in median time to shock control with the early administration of norepinephrine was slightly >1 hour, the change in time for the 75th percentile was close to 3 hours, and the impact on the 90th percentile is not reported. It is not unreasonable to think that if a morbidity or mortality benefit from establishing protocols to guide the early use of vasopressor in sepsis can be demonstrated, it would be because of the elimination of cases in which a significant delay in shock control occurred. Delayed administration of norepinephrine has been associated with increased mortality in retrospective reviews (2). In future trials looking at shock control, evaluations of the changes in time to control by quartile, not just mean time, are likely to increase the clinical applicability of the results. This is particularly true if the goal is to implement a protocol for management of shock in sepsis, as prior studies have shown an association between poor shock control and mortality (3).

There is clear need for a large, randomized trial to demonstrate the clinical significance of initiating vasopressors alongside or earlier during volume resuscitation before an argument can be made to change current practices. However, the CENSER (Early Use of Norepinephrine in Septic Shock Resuscitation) trial not only demonstrates proof of concept that early norepinephrine use leads to faster MAP control but also provides insights into the pharmacokinetic nature of this effect and its implications for the extremes of patient care. ■

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## Reply to El Bèze *et al.* and to Tung and Crowley

*From the Authors*:

The CENSER (Early Use of Norepinephrine in Septic Shock Resuscitation) trial examined whether administering low-dose



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