EVMS Emergency Medicine Journal Club
Therapy Worksheet

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Citation: Permpikul C, et al, **Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER). A Randomized Trial.** Am J Respir Crit Care Med. 2019 May 1;199(9):1097-1105.

Objective: To evaluate the hypothesis that early low-dose norepinephrine in adults with sepsis with hypotension increases shock control by 6 hours compared with standard care.

Methodology *(design, inclusion and exclusion criteria, interventions compared, outcomes evaluated*)
This was a prospective randomized double-blind placebo-controlled phase II clinical trial. It was conducted at Siriraj Hospital (national tertiary referral center) in Bangkok, Thailand over a 4 year period from 2013-2017. Data analysis was completed by the principal investigator and statistician, both of whom were blinded to the enrollment and treatment process.

Inclusion Criteria: Adults aged 18 or older who presented to the ED with hypotension (MAP<65) and infection as suspected cause were eligible for enrollment.

Exclusion Criteria: Patients who met septic shock criteria (by Surviving Sepsis) for greater than 1 hour before randomization, those who had acute CVA, ACS, pulmonary edema, status asthmaticus, active cardiac arrhythmia, active GI bleeding, pregnancy, seizure, drug overdose, burn injury, trauma, advanced stage cancer or those requiring immediate surgery were excluded.

456 patients were evaluated, of those 320 Eligible patients were randomly assigned into either early NorEpi or placebo group. Of these 320, 7 and 3 participants in each group respectively withdrew consent resulting in 155 patients included in each intention to treat analysis group. Investigators, patients, patient's families, physicians and nursing staff were blind to the patient assignment.

Identically packaged norepinephrine or placebo (D5W) was transfused at a rate to achieve a norepinephrine dose of 0.05mcg/kg/min via CVL or peripheral line for 24 hours without titration. These were prepared by a pharmacist who had no other role in the study. In addition, all patients received standardized treatment for septic shock according to Surviving Sepsis, including crystalloid solution, source control, and appropriate antibiotics. If hypotension had not resolved after 30ml/kg of fluid was infused provider choice vasopressor use was permitted.

Primary outcome: "Sustained shock control" as defined by 2 measurements q15m MAP of 65 with evidence of adequate tissue perfusion (0.5ml/kg/hr of urine for 2 consecutive hours OR decreased serum lacate by 10%) at 6 hours after diagnosis of sepsis with hypotension.

Secondary outcomes: 28 day mortality and in hospital mortality, rate of respiratory failure requiring mechanical ventilation, renal failure requiring RRT. Safety outcomes were also measured including new onset arrhythmia, organ ischemia, cardiogenic or noncardiogenic pulmonary edema.

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Statistical analysis was a Wilcoxon rank sum test for continuous variables and a chi-square test or Fisher exact test for categorical variables. Enrollment of greater than 150 participants per group provided adequate power to assess primary outcome.

	Comments
A. Are the results of the study valid? Answer questions below	
1. Were patients randomized?	Yes patients were randomized in a 1:1 fashion a using computer generated randomization table.
2. Was randomization concealed (Blinded)	Yes, the randomization processes was preformed by an investigator who had no other role in patient enrollment or management.
3. Were patients analyzed in the groups to which they were randomized?	Yes, analysis took place following randomization and intention-to-treat analysis occurred (p1099) in those who were randomized but did not complete.
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	For the most part yes, similar comorbidities were noted between groups, excepting that the norepinephrine group had a much less incidence of CKD (27 vs 37). Similar APACHE II scores, similar distribution of infectious source was noted as well. Vital signs including MAP, HR, Tmax were very similar, as were initial lactate.
C. Did experimental and control groups retain a similar prognosis after the study started (answer the questions below)?	
1. Were patients aware of group allocation?	No, patients and their families were kept blind to their group allocation.
2. Were clinicians aware of group allocation?	No physicians were blind to group allocation, however in the discussion it is noted that the rapid rise of BP following administration of the unlabeled norepinephrine likely “clued” astute physicians into the presence of the medication.
3. Were outcome assessors aware of group allocation?	No they were not.

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4. Was follow-up complete?	Yes, it appears that no patients were lost to follow-up.
D. What were the results?	
1. How large was the treatment effect? (difference between treatment and control group).	Regarding the primary outcome (shock control rate) the early norepi group was significantly higher. 76.1% versus 48.4% with an odds ratio of 3.4 (95% CI 2.09-5.53). For achievement of target map, urine output and lactate clearance all were significantly higher in norepi group P<0.05. There was no measured improvement in 28 day mortality 15.5% vs. 21.9%, RR 0.79 (95% CI 0.53 to 1.11) (P=.15) or in hospital mortality (P=.69) 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). There was no difference in need for mechanical ventilation or renal replacement therapy between the two groups, and no difference in organ support-free days to day 28.
2. How precise was the estimated treatment effect at a 95% confidence interval?	See above
D. How can I apply the results to patient care	
IV. Were the study patients similar to my patients?	Unlikely, this was a single center study in a homogenous population of Bangkok residents. Their rates of HTN (49%), DM (32%), CAD (16%) seem significantly lower than in our patient population though they were fairly high. A higher percentage of their patients went to a medical ward than ours which theoretically could portend even better results.
1. Were all clinically important outcomes considered?	This study primarily looked directly at MAP and perfusion markers as a surrogate for improving control of sepsis which are reasonable surrogates. Patient centered outcomes were secondary such as renal replacement therapy, mortality, mechanical ventilation. They did not include ICU or hospital days.

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2. Are the likely treatment benefits worth the potential harms and costs?	I believe so, especially in a euvolemic or hypervolemic septic patient. The theoretical harm of using Norepinephrine in volume depleted patients causing decreased perfusion to the digestive and renal system via vasoconstriction was not shown in this study, although was not measured directly. A real consideration is the cost/personnel concern that patients on norepinephrine automatically require ICU admission, adding to the cost of their hospitlizaiton. Frequently hypovolemic septic patients can be stabilized in the ED with fluids and antibiotics and safely admitted to a intermediate care unit.

Limitations:
-The largest limitation of this study is that the primary outcome was not patient centered. -This study was preformed in a single center, with a population that is likely different from our own.
-Fluid resuscitation rate was also not controlled.
-Response to early vasopressor may have served to unmask patients.

Clinical Bottom Line: Overall I felt that this was a reasonably well designed initial study to evaluate the use of early low dose norepinephrine in the ED. The statistically significant benefit in MAP as well as end organ perfusion likely outweighs the cost of the medication as well as the concern for splanchnic hypoperfusion. Many of the secondary outcomes/endpoints were better in the norepinephrine group, although not statistically significant in this small study. Larger, multicentered studies across different populations would be helpful in making this a standard of care in hypotensive septic patients however it is something I will certainly consider with my next patient.