Critical Review Form
Prognosis

PGY-3

Morimatsu H, Singh K, Uchino S, Bellomo R, Hart G. Early and exclusive use of norepinephrine in septic shock. Resuscitation. 2004 Aug;62(2):249-54.

Objectives: **To evaluate "the role of NE used as *single* agent *early* in septic shock." (p. 250)**

Methods: **This retrospective, cohort study was conducted in the intensive care unit (ICU) of the Austin and Repatriation Medical Centre in Melbourne, Australia over a 36-month period. Consecutive patients admitted to the ICU meeting criteria for sepsis with a mean arterial pressure (MAP) < 70 mmHg despite fluid resuscitation or MAP < 60 mmHg irrespective of fluid resuscitation. All patients were started on a norepinephrine drip at 2-5 µg/min, titrated to achieve a MAP > 75 mmHg.**

Patients underwent serial arterial blood gas, electrolyte, and lactate measurements on admission and every 4-6 hours. Fluid resuscitation was administered to keep right atrial pressures between 9 and 12 mmHg using colloid solution.

After excluding 51 patients (26.4% of the total) due to the use of inotropes, there were 142 patients included in the cohort. The median age was 65.9 years and 62% were male. The median MAP when norepinephrine was started was 60 mmHg.

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients representative?** *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	No. This study specifically enrolled patients admitted to the ICU with septic shock with either a MAP < 70 mmHg after fluid resuscitation, or a MAP < 60 mmHg irrespective of fluid resuscitation. Patients were not enrolled from the emergency department, but were instead patients already in the ICU. Many of these patients likely developed sepsis while in the hospital, which would result in more rapid care than those whose infections developed at home (external validity). The criteria for sepsis were unfortunately not well-defined; specifically, the authors do not mention how

		the presence of absence of an infectious cause for hypotension was determined.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	Uncertain. The authors do not provide much information regarding initial vital signs or initial lactate levels and the ranges associated with these values. The standard deviations associated with the SAPS-II and SOFA scores suggest a fairly wide range of disease severity, but this would still likely represent a sufficiently homogenous cohort of patients to evaluate the efficacy of the treatment of interest.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	Yes. All patients were followed through the entirety of their hospital stay and hence had complete follow-up data available.
D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	Yes. The outcomes assessed included mortality, need for renal replacement therapy, and change in blood pressure, all of which are completely objective.
II.	**What are the results?**	
A.	**How likely are the outcomes over time?** *For the defined follow-up period, how likely were subjects to have the outcome of interest.*	• Overall ICU survival was 69.7% (95% CI 61.7% to 76.7%) and hospital survival was 65.5% (57.3% to 72.8%). • Mortality was higher in more severely ill patients; among those with a SAPS II score > 56, hospital mortality was 50%. • The authors report significant reductions in mortality when compared to predicted mortality stratified by SAPS II score, however it is unclear where these predicted values come from. • Median ICU length of stay was 8 days (IQR 4 to 12 days). Median hospital length of stay was 23 days (IQR 12 to 41 days). • Renal replacement therapy was required in 20.4% of the cohort during their ICU stay.
B.	**How precise are the estimates of likelihood?**	See above. Confidence intervals were quite wide due to the small sample size.

	In other words, what are the confidence intervals for the given outcome likelihoods?	
III.	**How can I apply the results to patient care?**	
A.	**Were the study patients and their management similar to those in my practice?**	No. This study enrolled patients already admitted to the ICU of a single center in Australia, rather than patients presenting to the ED. This would likely lead to much more rapid treatment of sepsis than patients whose symptoms developed prior to hospital arrival. Additionally, this study was conducted prior to 2004, during a time in which sepsis care was focused on early goal-directed therapy. Management of sepsis has changed significantly since then and this would likely affect the efficacy of the timing of norepinephrine infusions. Patients also received primarily colloids, which are not typically used in the management of sepsis at this time.
B.	**Was the follow-up sufficiently long?**	Yes. All patients were followed through the entirety of their hospital stay. While the authors could have considered longer-term outcomes, the outcomes they assessed seem adequate given the nature of the study.
C.	**Can I use the results in the management of patients in my practice?**	No. This study suggests that mortality among patients treated with early norepinephrine with ongoing fluid resuscitation would have lower mortality than predicted, but provide no information regarding how they determine these predicted mortality rates. These patients were not compared to a similar cohort of patients who did not receive early norepinephrine, and hence it is not possible to determine the effect of this treatment on any patient-important outcomes.

Limitations:

1. **Patients were not enrolled from the emergency department, but were instead patients already in the ICU. Additionally, this study was conducted prior to 2004, and management of sepsis has changed significantly since then and this would likely affect the efficacy of the timing of norepinephrine infusions. (external validity).**

2. **This was a retrospective cohort study in which the details of chart review were not properly reported (Gilbert 1996 and Worster 2004).**

3. **The authors report significant reductions in mortality when compared to predicted mortality stratified by SAPS II score, however it is unclear where these predicted values come from.**

Bottom Line

This retrospective cohort study conducted in the ICU of a single hospital over a 36-month period during the early 2000s found that early administration of norepinephrine in septic shock during ongoing fluid resuscitation led to an overall ICU mortality of 30.7% and hospital mortality of 34.5%. Approximately one in five patients required renal replacement therapy. Unfortunately, this cohort was not compared to a group of patients who did not receive early norepinephrine, making it impossible to determine a treatment effect.