Critical Review Form
Therapy

PGY-1

Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, Dong Y, Xu L, Li N. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 2014 Oct 3;18(5):532.

Objectives: **To examine "the relationship between delay in initial norepinephrine administration and hospital mortality and investigated the effects of early norepinephrine administration on septic shock." (p. 2)**

Methods: **This retrospective chart review was conducted in two general surgical intensive care units (ICUs) of Jinling Hospital in Nanjing, China between January 2011 and December 2012. Adults patients (age 18 years or older) with a diagnosis of septic shock (defined at the presence of an infection with systemic manifestations and a systolic blood pressure [SBP] < 90 mmHg, a decrease of 40 mmHg in SBP from baseline, or a MAP < 65 mmHg despite resuscitation with 30 mL/kg of crystalloid fluid) were eligible for inclusion.**

The exposure being measured was time from onset of sepsis shock to initial administration of norepinephrine, which was dichotomized into early administration (Early-NE group, < 2 hours from onset of septic shock) and late administration (Late-NE, ≥ 2 hours from onset of septic shock. The primary outcome being evaluated was 28-day mortality.

Effective antimicrobial therapy was defined as first administration of an antibiotic to which the identified pathogen was susceptible or that matched national guidelines when cultures were negative, so long as administration was within 6 hours of the onset of septic shock. Documented infection was defined as identification of a plausible pathogen from the blood or infection site with a compatible syndrome, infection supported by a definitive surgical, radiologic, or pathologic diagnosis.

A total of 213 patients were included in the final analysis. All included patients received norepinephrine as the initial vasopressor. The overall 28-day mortality was 37.6%. The mean APACHE-2 score was 28.4. An infection was documented in 89.7% of cases. The mean time to initial norepinephrine administration was 3.1 hours; there were 126 patients (59.2%) in the early-NE group.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	

1.	Were patients randomized?	No. This was an observational study in which group allocation was determined by the timing of initiation or norepinephrine, which would be a the discretion of treating physicians and likely the results of multiple clinical factors. This study is therefore at a high risk of selection bias.
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	N/A. Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	N/A. Patients were analyzed based on the timing of norepinephrine administration, but this was not a randomized controlled trial.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Uncertain. Patients were similar with respect to age, gender, baseline APACHE II score, documented infection, and infectious source. Patients in the Early-NE group had a somewhat higher mean initial lactate (5.0 vs. 4.4). Unfortunately, several important pieces of information were not provided for the groups, including baseline vitals signs, medical comorbidities, and indication for ICU admission (e.g. trauma, surgery, etc.).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. This was retrospective study, making blinding impossible. It is unlikely, given the outcomes, that performance bias on the part of the patients would have affected the outcomes.
2.	Were clinicians aware of group allocation?	Yes. As above, clinicians were not blinded due to the retrospective nature of this study, as well as the intervention being assessed (timing of norepinephrine administration). Given that this was retrospective, it is unlikely that performance bias on the part of clinicians would have any impact on outcomes.
3.	Were outcome assessors aware of group allocation?	Likely yes. The authors make no mention of blinding of chart reviewers or outcome assessors. However, given the very objective nature of the

		outcome (mortality), observer bias should not have influenced the results.
4.	Was follow-up complete?	Yes.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• 28-day mortality was higher in patients in the Late-NE group compared to the Early-NE group, with an odds ratio (OR) of 1.86 (95% CI 1.04 to 3.34). • For every hour delay in initiation of a norepinephrine infusion, the OR for death was 1.20 (95% CI 1.07 to 1.35), corresponding to a 20.4% increase in the risk of death. • There was no significant difference in ICU length of stay between the two groups.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	No. While this study evaluated patients meeting criteria for septic shock with hypotension, patients were solely recruited in a surgical ICU. It would appear that all patients in the study developed sepsis during their hospital stay, and hence therapy would have been initiated much more rapidly than patients presenting to an emergency department with sepsis of potentially longer duration. In addition, these patients were seen in the setting of trauma and recent surgery, and hence would have very different sources of sepsis than many of the patients treated in our emergency department.
2.	Were all clinically important outcomes considered?	No. A limited set of outcomes was assessed, including mortality, change in BP and lactate over time, and ICU length of stay. Hospital length of stay, need for mechanical ventilation, need for renal replacement therapy, and other signs of organ failure were not evaluated.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This small, observational study was conducted in a retrospective, nonrandomized fashion, and hence would he highly susceptible to selection bias. These findings, while significant, would need to be further evaluated in a larger,

		randomized controlled trial in order to confirm the results.

Limitations:

1. **This was a retrospective, observational study at high risk of selection bias. Despite the two groups appearing to be similar with respect to most prognostic factors, it is never possible to account for unknown confounders.**

2. **This study largely included patients with sepsis related to recent trauma or surgery and subjects were enrolled entirely from a surgical ICU and not the emergency department (external validity).**

3. **No information was provided regarding who abstracted data from the medical record, or what sort of form was used to record abstracted data (Gilbert 1996 and Worster 2004).**

4. **A limited set of outcomes were assessed. This did not include need for mechanical ventilation, need for renal replacement therapy, and other signs of organ failure.**

Bottom Line:

This small, retrospective study conducted in two surgical ICUs at a single hospital in China found that among patients with septic shock with hypotension, delayed administration or norepinephrine (initiated 2 or more hours after developing sepsis) was associated with an increased risk of death, with an odds ratio (OR) of 1.86 (95% CI 1.04 to 3.34). For every hour delay in initiation of a norepinephrine infusion, the OR for death was 1.20 (95% CI 1.07 to 1.35), corresponding to a 20.4% increase in the risk of death. This study is at high risk of selection bias, and these results will need to be confirmed with further randomized controlled trials.