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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. ■

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

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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

Originally Published in Press as DOI: 10.1164/rccm.201905-1083LE on June 27, 2019

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Originally Published in Press as DOI: 10.1164/rccm.201906-1214LE on June 27, 2019

norepinephrine (NE) at the beginning of resuscitation for sepsis-induced hypotension would increase shock control by 6 hours as compared with standard care (1).

After reviewing the results, Tung and Crowley mentioned that the average dose of NE required to achieve the mean arterial pressure goal of 65 mm Hg was 0.1 μg/kg/min, whereas in the intervention arm, the dose of NE was 0.05 μg/kg/min. We agree with this comment. This observation provides not only a hint for the next study but also a possible explanation for the insignificant reduction in the amount of fluid given in the early-NE group. However, certain concerns include the fact that the administration of a higher initial dose of NE requires more careful attention to the peripheral venous site, and placement of the central venous catheter during intravascular volume depletion at the beginning of resuscitation may also be problematic. In their second comment, they noted that the impact of the intervention was not very strong in patients in the 75th percentile. This should be explained by the patients' heterogeneity. Those who had a serious infection or underlying cardiovascular disease may not have responded well to resuscitation.

In their first comment, El Bèze and colleagues noted that epinephrine was used in our study in a higher proportion of patients than in other studies. It was assumed that the mean dose of NE used before initiating epinephrine was 0.15 μg/kg/min. Actually, our guidelines recommend the use of epinephrine when the NE dose approaches 0.2 μg/kg/min, or when metabolic acidosis is present. The assumed dose was quite close to the recommended one. With regard to their comment about the use of vasopressors during resuscitation in the control group, we note that open-label NE was allowed to start when the blood pressure goal was not reached after optimal fluid resuscitation. The dose adjustment of NE was recommended to be 0.01–0.02 μg/kg/min every 15 minutes. The dosage plots were thus paralleled, as shown in Figure E3B in the online supplement of Reference 1. As for their comment on the sources of sepsis, in which urinary tract infection (UTI) was more prevalent than pneumonia, we note that the sources of infection vary among studies. In our study, the proportions were 23.9–25.8% pneumonia, 29–30.3% UTI, and abdominal infection 20–21.3% (1). In the study by River and colleagues, the proportions were 39.5–38.5% pneumonia, 27.7–25.6% UTI, and 4.2–3.4% abdominal infection (2). Yealy and colleagues reported proportions of 31.9–34.1% pneumonia, 20.2–22.8% UTI, and 11.2–15.7% abdominal infection (3), and Asfar and colleagues' study had 51.5–52.1% pneumonia, 11.3% UTI, and 16.8–17.3% abdominal infection (4). ■

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

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