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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

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