Lactate-Guided Resuscitation Strategies in Septic Shock: Differentiating the Bad From the Unexceptional

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Guest Contributors

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Editor's Note: *You are reading the 71st installment of* Annals of Emergency Medicine *Journal Club. As the Journal Club enters its second decade of publication, the format has been revised and will focus on a monthly succinct review of high-impact articles from this journal and other premier medical journals relevant to emergency medicine. The reviews are followed by questions demonstrating principles by which readers—be they clinicians, academics, residents, or medical students—may critically appraise the literature. We are interested in receiving feedback about this feature. Please e-mail journalclub@acep.org with your comments.*

ARTICLE IN REVIEW

Hernández G, Ospina-Tascón GA, Damiani LP, et al. Effect of a resuscitation strategy targeting peripheral perfusion status vs serum lactate levels on 28-day mortality among patients with septic shock: the ANDROMEDA-SHOCK randomized clinical trial. *JAMA*. 2019;321:654-664.

What Question Did This Investigation Aim to Answer?

Is a resuscitation strategy that targets capillary refill time superior to a lactate-guided approach in the management of patients presenting in septic shock?

What Study Design Did the Authors Choose?

Design: Multicenter randomized open-label design.

Trial registry number: NCT03078712.

Setting: ICU.

Population: Adult patients older than 18 years with septic shock who were admitted to the ICU. Septic shock was defined as suspected or confirmed infection, with an initial serum lactate level of greater than or equal to 2.0 mmol/L and requirements of vasopressors to maintain a mean arterial pressure of 65 mm Hg after initial resuscitation efforts of intravenous fluids at at least 20 mL/kg.

Intervention: Patients were randomized to have continued resuscitative efforts guided by capillary refill time (peripheral perfusion approach) or serum lactate levels (lactate level–targeted resuscitation).

Primary Outcome: Twenty-eight-day mortality.

Secondary Outcomes: Ninety-day mortality, organ dysfunction during the first 72 hours, mechanical ventilation–free days, renal replacement therapy–free days, vasopressor-free days, and ICU and hospital length of stay.

Sponsors: This study received logistic support from the Pontificia Universidad Católica of Chile.

What Did the Authors Find?

During a 1-year period, the authors enrolled 424 patients from 28 sites, and the majority (71%) were enrolled from the emergency department (ED). A lactate-guided strategy led to a higher volume of fluid administered, more vasopressor use, and more frequent use of epinephrine. But this failed to translate into an improvement in clinical outcomes. In fact, when patients received lactate-guided strategy, they tended to fare worse compared with those receiving a perfusion-targeted approach. The 28-day mortality was 34.9% in the peripheral perfusion group and 43.4% in the lactate-guided group (hazard ratio 0.75; 95% confidence interval [CI] 0.55 to 1.02; P=.06). This –8.5% absolute difference (95% CI −18.2% to 1.2%), although not statistically significant, bordered on demonstrating harm associated with a lactate-guided resuscitation approach. In fact, there was significantly less organ dysfunction at 72 hours in the peripheral perfusion group, which points to a biologically plausible explanation for a difference in mortality.[1]

How Did the Authors Interpret the Results?

For patients with septic shock, a resuscitation strategy targeting normalization of capillary refill time, compared with a strategy targeting serum lactate levels, did not reduce all-cause 28-day mortality.

DISCUSSION POINTS

1. *Hernández et al[2] reported an 8.5% absolute difference in 28-day mortality in favor of the peripheral perfusion*

resuscitation strategy. Describe statistical power. How is it calculated?

Statistical power is the ability of a trial to reject the null hypothesis and detect a difference between 2 groups when a true difference exists.[3] It can be conceptualized as the ability to separate true-positive study results from false-negative ones, or, put another way, the sensitivity of a trial under a set of assumptions and sample size. Traditionally, an acceptable statistical power has been set at 80% or 90%, although when an outcome such as mortality is involved, perhaps a lower threshold is worth consideration. Readers interested in more detailed discussion on this topic may reference the March 2008, March 2014, and November 2015 Journal Clubs, available at http://annemergmed.com.[4-6]

Calculated power and study precision are closely related, but the distinctions between the two are important. Power is used to calculate estimated study sample sizes *before* conduct of a study to better gauge cost and feasibility of conducting it; without sample size calculations that incorporate assumptions about power, patients could be enrolled in futilely small studies that cannot answer the scientific question of interest, which is unethical and a waste of resources. Precision, in contrast, can be thought of as an assessment of power *after* a study has been completed. Precision is most often presented as 95% CIs and is closely related to the number of patients and the variability of the measure of interest in that specific study.

Hernández et al[2] based their sample size calculation (ie, estimate) on several assumptions. One assumption was that 15% was the smallest clinically important difference in 28-day mortality between treatment groups. Another assumption was that 90% power is acceptable (ie, that the 10% chance that the calculated sample size would not detect a real difference in mortality between the treatment group was an acceptable balance against the cost of enrolling more patients to increase power). If the trial did in fact find greater than or equal to 15% lower mortality in patients randomized to the peripheral perfusion strategy, this effect size could range as low as 6% or as high as 23.9%. The authors reported an 8.5% absolute risk reduction in 28-day mortality favoring the peripheral-perfusion group. The 95% CI surrounding this risk reduction was –18.2% to 1.2%. The width of the CI around the difference defines the precision of the study. A larger sample size would have increased the statistical precision, decreasing the CI surrounding the point estimate.

To retrospectively state a trial is underpowered once the results of the study are known is somewhat disingenuous. The claim that the observed difference is true and only failed to reach statistical significance because of an inappropriately small sample size may in fact be correct, but is not justifiable because of the data alone. Any post hoc power calculation performed on such a data set will inevitably demonstrate the limited ability to differentiate a true difference from the null hypothesis.[7] Once the trial results are obtained, post hoc analyses should be avoided and when they are conducted should be clearly identified as post hoc and exploratory. Instead, the focus should be on the width of CIs around point estimates for a more honest interpretation of the data.[1] In this case, when a peripheral perfusion resuscitation strategy is used in place of a lactate-guided approach, we are unable to differentiate an 8.5% reduction in mortality from no effect.

2. *Given what we know about statistical power, how should these results be interpreted?*

There are a number of conclusions that can be drawn from these results. One could conclude that there is no difference between these 2 resuscitative strategies and that either approach to the early hemodynamic management of patients in septic shock is adequate. An alternative interpretation is that there is evidence of harm from the lactate-guided therapy, even though the sample size was too small to detect an absolute difference in 28-day mortality of less than 15%. From a biological and mechanistic standpoint, the majority of lactate produced in the early stages of sepsis is not due to lack of end-organ perfusion, which leads us to question its inclusion in a treatment algorithm that treats it as a marker of tissue hypoxia.[8]

3. *Currently, clinicians practicing in the United States are mandated by the Centers for Medicare & Medicaid Services to incorporate lactate in their SEP-1 sepsis compliance measure, requiring clinicians to draw blood to establish an initial lactate level and to repeat the test when results are elevated in their 3-hour sepsis bundle. How should this study affect this compliance measure?*

Overall ED compliance with the SEP-1 Centers for Medicare & Medicaid Services mandate is poor. Studies cite wide variations in compliance, with some reporting it to be as low as 8.7%.[9,10] Of the 4 performance measures included in the 3-hour bundle, repeated lactate measurement was met least often.[10] As discussed, we are unable to state that a lactate-guided approach is inferior to a peripheral perfusion approach, and it is safe to say it is no better. With no evidence that it improves patient-important outcomes, a government mandate requiring lactate-guided resuscitation strategy adds needless logistic complexity to the already overburdened ED work flow, and it may encourage overresuscitation and the downstream harms associated with such aggressive strategies.

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