PGY-3

**Critical Review Form**

 **Therapy**

[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 Feb 19;321(7):654-664.](http://pmid.us/30772908)

**Objectives: "a multicenter randomized clinical trial comparing peripheral perfusion–targeted resuscitation to lactate level–targeted resuscitation in patients with early septic shock was conducted, hypothesizing that resuscitation guided by peripheral perfusion would be associated with improved outcomes." (p. 655)**

**Methods: This multicenter, randomized controlled trial was conducted at 28 hospitals in 5 countries in South America between March 2017 and March 2018. Consecutive adult patients (≥ 18 years) who were admitted to the ICU with septic shock were eligible for enrollment. Septic shock was defined as the presence of a suspected infection plus a lactate ≥ 2.0 mmol/L and need for vasopressors following fluid resuscitation to maintain a mean arterial pressure (MAP) ≥ 65 mmHg. Patients were randomized in a 1:1 fashion to peripheral perfusion-targeted resuscitation or lactate level-targeted resuscitation.**

**Peripheral perfusion was measured by capillary refill time (CRT) using a standardized method and all centers were trained prior to the start of the study. This was measured every 30 minutes until normalization, and then every hour. Lactate levels were measured every 2 hours. The intervention period in both groups was 8 hours. Both groups were managed with an identical protocolized approach to resuscitation that involved 500 mL crystalloid fluid challenges every 30 minutes based on either CRT or lactate levels (depending on patient group), vasopressor adjustment in patients with chronic hypertension, and an "inodilator test" with low-dose dobutamine or milrinone.**

**The primary outcome was all-cause mortality at 28 days. Secondary outcomes included death within 90 days, organ dysfunction within 72 hours of randomization (by** [**SOFA score**](https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score)**), mechanical ventilation-free days within 28 days, renal replacement-free days within 28 days, vasopressor-free days within 28 days, and ICU and hospital length of stay.**

**A total of 424 patients were enrolled, with a mean age of 63 years; 53% were female. Two hundred and twelve patients were assigned to each group.**

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| **Critical Review Form: Therapy** |
| Guide | Comments |
| **Are the results valid?** |
| **Did experimental and control groups being the study with a similar prognosis?** |
| Were patients randomized? | Yes. Patients were randomized in a 1:1 fashion to either peripheral perfusion-targeted resuscitation or lactate level-targeted resuscitation. |
| Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be “randomized” to a particular group? | Yes. "A randomization sequence by permuted blocks of 8 with an allocation of 1:1 was generated by a computer program. Allocation concealment was maintained by means of central randomization. Investigators called a representative of the study coordinating center, who was available via a dedicated telephone line. Group allocation was only disclosed after the information was centrally checked and recorded." (p. 655) |
| Were patients analyzed in the groups to which they were randomized? | Yes. All patient were analyzed according to an [intention-to-treat protocol](http://pmid.us/10480822). Lack of adherence was seen in 29 patients in the peripheral perfusion group and 23 patients in the lactate group. There were 8 patients who did not receive the assigned intervention at all. All patients were analyzed according to the group to which they were randomized. |
| Were patients in the treatment and control groups similar with respect to known prognostic factors? | Yes. Patients were similar with respect to age, gender, baseline APACHE II score, baseline SOFA score, infectious source, baseline vital signs, and baseline perfusion-related variables. |
| **Did experimental and control groups retain a similar prognosis after the study started?** |
| Were patients aware of group allocation? | Yes. Given the intervention being assessed, blinding would not have been feasible. It is unlikely that [performance bias](http://bmg.cochrane.org/assessing-risk-bias-included-studies) on the part of patients would have affected outcomes. |
| Were clinicians aware of group allocation? | Yes. As noted above, blinding of clinicians would not have been possible given the nature of this study. It is possible that [performance bias](http://bmg.cochrane.org/assessing-risk-bias-included-studies) on the part of clinicians would have affected outcomes or that a [Hawthorne effect](https://catalogofbias.org/biases/hawthorne-effect/) may have been observed. Importantly, CRT and serial lactate levels were measured in both groups, without blinding, and either finding may have guided resuscitation despite an individual patient's group allocation.  |
| Were outcome assessors aware of group allocation? | Yes. No attempt was made to blind outcome assessors to treatment group. |
| Was follow-up complete? | Yes. "Data for the primary and secondary outcomes were obtained for all patients." (p. 657) |
| **What are the results?** |
| How large was the treatment effect? | * 28-day mortality was lower in the peripheral perfusion group (34.9%) than in the lactate group (43.4%), though this difference did not achieve statistical significance: hazard ratio 0.75, 95% CI 0.55 to 1.02.
* There was less organ dysfunction at 72 hours in the peripheral perfusion group: mean difference in SOFA score -1.00, 95% CI -1.97 to -0.02.
* There was no difference in death at 90 days: absolute difference -5.7%, 95% CI -15.6 to 4.2.
* There was no significant difference in mechanical ventilator-, renal replacement-, or vasopressor-free days within 28 days between the groups. There was also no difference in ICU or hospital length of stay.
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| How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?) | See above. |
| **How can I apply the results to patient care?** |
| Were the study patients similar to my patient? | Likely yes. While this study was conducted in several hospitals in South America, the comorbidities provided and sources of infection in this cohort of patients with septic shock is likely very similar to patients we see with septic shock in our institution. Treatment strategies in ICUs in these countries are also likely similar to those utilized for such patients in our ICUs. |
| Were all clinically important outcomes considered? | Yes. The authors considered mortality at various timeframes, need for mechanical ventilation, renal replacement therapy, and vasopressors, and length of stay in the ICU and hospital. |
| Are the likely treatment benefits worth the potential harm and costs? | Yes. While there does appear to be some reduction in mean SOFA scores with peripheral perfusion-based resuscitation compared to lactate-based resuscitation, this was a secondary outcome and should be considered hypothesis-generating rather than management-changing. Given that there was no worsening in outcomes, and actually a trend toward improved 28-day mortality, use of peripheral perfusion to guide resuscitation in septic shock seems reasonable, particularly in settings where serial lactate measurement is not feasible. My primary concern with this study is that lack of blinding may have led to performance bias and a possible Hawthorne effect. Unfortunately, a blinded study would not be feasible given the nature of the intervention. |

**Limitations:**

1. **Given the nature of the intervention, blinding of clinicians would not have been possible. It is possible that** [**performance bias**](http://bmg.cochrane.org/assessing-risk-bias-included-studies) **on the part of clinicians would have affected outcomes or that a** [**Hawthorne effect**](https://catalogofbias.org/biases/hawthorne-effect/) **may have been observed.**
2. **The study was conducted in several hospitals in 5 South American countries. Possible differences in patient comorbidities and standard-of-care could make it difficult to generalize the results (**[**external validity**](http://www.epmonthly.com/archives/features/understanding-external-validity/)**).**
3. **Given the trend toward a clinically meaningful difference in the primary outcome that did not achieve statistical significance, this study was likely** [**underpowered**](http://pmid.us/12117401)**.**

**Bottom Line:**

**This unblinded, multicenter, randomized controlled trial found that patients with septic shock resuscitated using on a peripheral perfusion-based protocol had a trend toward reduced 28-day mortality (hazard ratio 0.75, 95% CI 0.55 to 1.02) and a significant reduction in organ dysfunction compared to those managed using serial lactate levels. The unblinded nature of the study potentially introduced performance bias and a Hawthorne effect that could have led to improved outcomes.**