PGY-4

**Critical Review Form**

 **Therapy**

[Kattan E, Hernández G, Ospina-Tascón G, et al; ANDROMEDA-SHOCK Study Investigators and the Latin America Intensive Care Network (LIVEN). A lactate-targeted resuscitation strategy may be associated with higher mortality in patients with septic shock and normal capillary refill time: a post hoc analysis of the ANDROMEDA-SHOCK study. Ann Intensive Care. 2020 Aug 26;10(1):114.](http://pmid.us/32845407)

**Objectives: "Our primary aim was to determine if septic shock patients evolving with normal CRT at T2 exhibited a higher mortality and organ dysfunction after being randomized to the LT [lactate-targeted] arm at T0 than when randomized to the CRT [capillary refill time] arm. Our secondary aim was to determine if those septic shock patients evolving with normal CRT at T2 received more therapeutic interventions when randomized to the LT arm at T0 than when randomized to the CRT arm." (p. 2)**

**Methods: This is a *post hoc* analysis of a multicenter, randomized controlled trial 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.**

**The intervention period in both groups was 8 hours. CRT was measured every 30 minutes in the CRT group until normalization, and then every hour thereafter. In the LT group, lactate levels were measured every 2 hours. Both groups were managed with an identical protocolized approach to resuscitation that involved 500 mL crystalloid fluid challenges every 30 minutes, vasopressor adjustment in patients with chronic hypertension, and an "inodilator test" with low-dose dobutamine or milrinone.**

**In this analysis, the authors focused on CRT status at 2 hours after randomization (T2), looking at interventions and outcomes for the entire cohort and based on study group allocation. They specifically compared outcomes for both groups (CRT and LT) when looking only at those patients with a normal CRT at T2, then at those patients who achieved a target lactate (normal level or 20% decrease) at T2. The primary outcome was mortality. The authors also looked at a composite outcome that included the cumulative number of "actions" taken (which included each 500 mL bolus of fluid, any vasopressor test, or any inodilator test) with each action assigned a value of 1.**

**The original study enrolled 424 patients, but only 378 had data available at T2 and were included in this analysis. At T2, 184 patients (49%) had a normal CRT. Of those wtih a normal CRT at T2, 102 were in the CRT arm compared with 82 in the LT arm.**

|  |
| --- |
| **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? | No. This was a *post hoc* analysis of data from a previous randomized controlled trial. By only including patients whose CRT normalized by T2, and excluding those whose CRT did not normalize, there is a high risk of introducing imbalance between the two groups being analyzed ([selection bias](http://pmid.us/21491415)). The authors attempted to account for certain known confounders by performing multivariate logistic regression, but this technique is flawed and does not account for [unknown variables](http://link.springer.com/chapter/10.1007/978-0-387-87959-8_5). |
| Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be “randomized” to a particular group? | N/A. |
| Were patients analyzed in the groups to which they were randomized? | No. Again, a large subset of patients originally randomized into the two groups was excluded from this analysis. |
| Were patients in the treatment and control groups similar with respect to known prognostic factors? | No. At T2, patients in the two groups (CRT and LT) appear to be similar with respect to age, gender, APACHE II score, SOFA score, Charlson Index, sepsis origin, baseline CRT, and baseline ScvO2. Baseline MAP appears to be lower in the LT group compared to the CRT group (67 vs. 70 mmHg, p = 0.01), but the clinical significance of this is uncertain. |
| **Did experimental and control groups retain a similar prognosis after the study started?** |
| Were patients aware of group allocation? |  |
| Were clinicians aware of group allocation? |  |
| Were outcome assessors aware of group allocation? |  |
| Was follow-up complete? |  |
| **What are the results?** |
| How large was the treatment effect? | * Patients who achieved a normal CRT at T2 received less resuscitative interventions, had a lower [SOFA score](https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score) at 24 hours (median 7 vs. 10), and had a lower 28-day mortality (30% vs. 46%) compared to those whose CRT remained abnormal, regardless of study group allocation.
* When looking only at patients with a normal CRT at T2:
	+ Patients in the LT arm had a higher 28-day mortality compared with those in the CRT arm (40% vs. 23%, RR 1.8, 95% CI 1.1 to 2.8).
	+ Patients in the LT arm also had more resuscitative interventions throughout the resuscitative intervention period than those in the CRT arm (median 3 vs. 1.25),
	+ Following multivariate logistic regression to balance for several confounding factors, allocation to the LT study group was associated with increased 28-day mortality (OR 3.3, 95% CI 1.5 to 7.1).
 |
| How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?) |  |
| **How can I apply the results to patient care?** |
| Were the study patients similar to my patient? |  |
| Were all clinically important outcomes considered? |  |
| Are the likely treatment benefits worth the potential harm and costs? |  |

**Limitations:**

1. **This was a *post hoc* analysis of data from a randomized controlled trial. The exclusion of patients whose CRT did not normalize by T2 has a high risk of creating imbalance between groups and introducing** [**selection bias**](http://pmid.us/21491415)**.**
2. **Don't know how much fluid received between T0 and T2 in the two groups**

**Bottom Line:**

**In this *post hoc* analysis of a previous randomized controlled trial, patients with septic shock with a normalized CRT after 2 hours of resuscitation appeared to fare worse when treated with a lactate-targeted strategy than when treated with a CRT-targeted strategy.**