**ESICM**
European Society of Intensive Care Medicine

# ANDROMEDA-SHOCK-2: Personalized Hemodynamic Resuscitation Targeting Capillary Refill Time in Early Septic Shock

## BACKGROUND

The optimal resuscitation strategy for patients with septic shock remains uncertain.

## RESEARCH AIM

To determine whether a personalised haemodynamic resuscitation strategy targeting capillary refill time (PHR-CRT) improves patient-centred outcomes.

## METHODS

**Design:**
- International, multicentric randomized trial including adult patients with septic shock

**Intervention:**
- Application of a PHR-CRT, incorporating pulse pressure, diastolic arterial pressure, fluid responsiveness, and echocardiography to guide the initial use (first 6 hrs) of fluids, vasopressors, and inotropes compared to standard of care (SOC); patients were randomized within 4 hrs of shock onset

**Primary endpoint:**
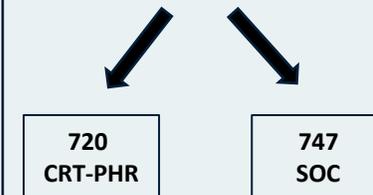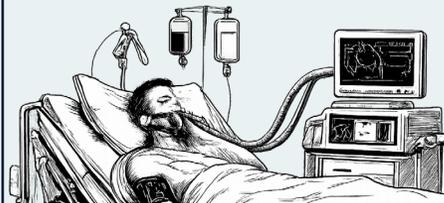Hierarchical composite at 28 days
including:
- Mortality,
- Duration of vital support,
- Length of hospital stay

**Statistical analysis:**
- Win-ratio

## Results

**Patients:**

- 1467 early septic shock pat.
- 86 sites in 19 countries
- 43.3% female



| 720 CRT-PHR | 747 SOC |
|---|---|

**Primary endpoint:**

Hierarchical composite at 28 days

Total wins
CRT-PHR 48.9%   SOC 42.1%

**Win ratio, 1.16 (95%CI 1.02-1.33, p=0.4)**

**Secondary endpoint:**

Outcomes at 28 days

|  | CRT-PHR | SOC | Effect |
|---|---|---|---|
| All-cause mortality | 26.5% | 26.6% | HR 0.99 (0.81–1.21) |
| Vital support-free days | 16.5±11.3 (mean±SD) | 15.4±11.4 | pOR 1.28 (1.06–1.54) |
| Hospital stay, days | 15.3±9.0 (mean±SD) | 16.2±9.4 | MD −0.85 (−1.80 to 0.10) |

**No differences in 28-day mortality but higher mean of vital support-free days**

## CONCLUSION

- **CRT**-targeted personalised resuscitation strategy in the initial 6 hrs of septic shock **outperformed usual care** for the 28-day composite outcome
- This finding was primarily **driven by reduced duration of organ support**.

## Time to rethink resuscitation goals in septic shock:

In this special edition of the *Point of View* series, the Inflammation and Sepsis Section presents its perspective on what it considers one of the most relevant sepsis papers among the new releases presented at the ESICM LIVES 2025 conference in Munich: Glenn Hernández's outstanding ANDROMEDA-SHOCK-2 trial demonstrating how the implementation of a capillary refill time (CRT)-targeted resuscitation algorithm may improve outcomes in patients with septic shock, thereby opening a new chapter in the pursuit of optimised resuscitation strategies [1].

Until today, there is a lack of evidence-based physiological targets for resuscitation in patients with septic shock, and their identification remains a topic of ongoing debate. In the landmark study published by Rivers and colleagues in 2001, a significant reduction in in-hospital mortality was reported when patients were treated according to a bundle of predefined targets, that at that time included CVP, MAP, ScvO2[2]. However, subsequent large validation trials failed to reproduce these findings, and thus only selected elements, such as maintaining a MAP = 65 mmHg, have persisted as recommended targets over the past decades, while others have largely fallen out of favour [3].

According to the current Surviving Sepsis Campaign guidelines, a MAP target of 65 mmHg and low lactate concentrations remain central goals within resuscitation protocols [4]. Nevertheless, the robustness of these targets in improving patient outcomes has been questioned. For example, in a major trial published in 2020, Françoise Lamontagne and colleagues demonstrated that a lower MAP target of 60–65 mmHg yielded comparable 90-day mortality outcomes to standard care in patients aged ≥ 65 years with distributive shock [5]. In 2025, Endo Akira showed in a comparable patient population from Japan that targeting a higher MAP of 80–85 mmHg was associated with an increased risk of mortality compared with a target of 65–70 mmHg, further challenging the "one-size-fits-all" philosophy underpinning current sepsis recommendations [6]. Additionally, it is very well possible that we are hunting the wrong target as pressure is really not equal to flow. At the end of the day, **resuscitation protocol should ultimately target tissue perfusion**.

Lactate, although widely used as a marker of anaerobic metabolism, has also some important limitations. Its kinetics are slow, and plasma concentrations are influenced not only by impaired tissue perfusion and oxygen delivery, but also by mitochondrial dysfunction, as well as impaired hepatic clearance. The first ANDROMEDA-SHOCK trial, published in 2019, demonstrated lower SOFA scores at 72 hours in a cohort of 424 patients with septic shock managed using a CRT-targeted resuscitation strategy compared with a lactate-guided approach; however, it failed to demonstrate a benefit in the primary outcome of 28-day mortality [7].

In the now released ANDROMEDA-SHOCK-2 trial, the investigators advanced this line of research by evaluating a resuscitation protocol targeting CRT normalisation by optimizing fluids and vasopressor use based on simple physiological assumptions compared with standard care in 1,467 patients with early septic shock. The algorithm is mostly influenced by two variables, i.e. pulse pressure as surrogate for volume depletion and diastolic pressure for vasoplegia. The protocol demonstrated superiority for a hierarchical composite endpoint comprising mortality, duration of organ support, and hospital length of stay, notably without the use of MAP or lactate targets. Secondary single-endpoint analysis revealed no significant difference in mortality but demonstrated a higher average number of vital support–free days. Although the study design does not allow precise determination of how much benefit was attributable to the specific multilayered physiological algorithm to guide fluid, vasopressor, and inotrope therapy, it clearly supports the concept that a clinically meaningful bedside parameters such as **CRT can effectively guide resuscitation in septic shock.** Notably, the increased use of dobutamine and the reduced need for resuscitation fluids highlight the critical role of inotropic support in achieving adequate perfusion in this patient population.



Systemic Inflammation and Sepsis

It is therefore **time to reconsider current practice** and shift our therapeutic focus towards clinically relevant indicators of tissue perfusion, and strategies to achieve them, rather than indirect and highly confounded surrogate markers such as fixed MAP thresholds and lactate targets.

1. ANDROMEDA-SHOCK-2 Investigators, JAMA 2025
2. Rivers, NEJM, 2001
3. The PRISM Investigators, NEJM, 2017
4. Evans, Intensive Care Med, 2021
5. Lamontagne, JAMA, 2020
6. Endo, Intensive Care Med, 2025
7. Hernández, JAMA, 2019

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