JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
Open Access
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

LETTER TO THE EDITOR

Emergency Medical Services

Check for updates

Sepsis Resuscitation: Caution Against Conflating Initial Fluid Resuscitation and Overall Sepsis Management

To the Editor:

We thank Toledo-Palacios et al[1] for taking the time to read our article "State of the art of sepsis care for the emergency medicine clinician," which is focused on the early phase of sepsis presenting to the emergency department (ED). We appreciate the thoughtful commentary focusing on the role of intravenous (IV) fluids in sepsis management. The authors present their perspective on restrictive fluid in sepsis management, though caution is advised when conflating this with initial resuscitation.

We note in the article that hypotension in the early phases of sepsis presentation is a marker of circulatory failure and an indicator of decreased relative preload. The Surviving Sepsis Campaign (SSC) suggestion of 30 mL/kg of crystalloid fluid for sepsis-induced hypoperfusion as the initial resuscitation approach is recommended within the first 3 hours of resuscitation. Toledo-Palacios et al[1] state that the SSC downgraded the recommendation for initial resuscitation from moderate to weak. In Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach principles, the quality of evidence is based on a multitude of domains, and a recommendation's strength reflects the extent to which a guideline panel's confidence in the evidence balances the continuum of desirable and undesirable effects and the quality of the evidence. The SSC emphasizes timely and effective fluid resuscitation as being crucial for stabilization in sepsis-induced hypoperfusion and provides a rationale for downgrading as being related to the quality of the evidence derived from observational studies with a lack of prospective interventional studies comparing different volumes for initial resuscitation. The panel nonetheless favored an initial resuscitation amount of 30 mL/kg and thus continued to list it as a recommendation.[2] Failure to administer 30 mL/kg of crystalloid fluids within 3 hours of the onset of sepsis-induced hypoperfusion is associated with increased odds of mortality (odds ratio [OR], 1.52; 95% confidence interval [95% CI], 1.03-2.24), delayed hypotension (OR, 1.42; 95% CI, 1.02-1.99), and increased intensive care unit (ICU) length of stay by approximately 2 days (B coefficient [B] = 2.0; 95% CI, 0.5-3.6).[3]

Studies focusing on sepsis fluid management have not evaluated the initial resuscitation phase. The CLASSICS and CLOVERS trials enrolled patients after the initial resuscitation phase, and thus, we agree with Toledo-Palacios et al[1] that this limits the interpretation of ideal approaches in initial resuscitation. As we have highlighted in our article, after the initial phase of resuscitation, the continuous assessment of the patient's condition with appropriate hemodynamic monitoring will determine whether more fluids or vasopressors are needed.

The shortages of IV fluid caused by natural disasters have forced health care systems to implement conservation strategies. The primary goal during such crises is to manage these shortages while minimizing adverse outcomes for patients. Decreasing the use of initial IV fluid resuscitation in patients with sepsis-induced hypoperfusion may, in fact, increase the risk of adverse outcomes.[3] Therefore, a more balanced conservation strategy would be to restrict fluids in patients without sepsis-induced hypoperfusion rather than in those with it.

Toledo-Palacios et al[1] suggest that the CLOVERS trial failed to demonstrate the superiority of liberal over restrictive therapy. The trial, though, was designed to evaluate the superiority of a restrictive fluid strategy (with early use of vasopressors) over a liberal fluid strategy during the first 24 hours of resuscitation. The aim was to show a beneficial effect of the restrictive fluid approach, but it was stopped early after the second interim analysis for futility when only two-thirds of the intended enrollment was completed. These results suggest that restricting fluid in favor of early vasopressor may result in harm. Although the trial does not evaluate whether 30 mL/kg is the ideal resuscitation amount, patients in the liberal fluid group received a median (IQR) of 2300 mL (2000-3000 mL) compared with the restrictive fluid strategy group receiving a median (IQR) of 500 mL (130-1097 mL) during the first 6 hours after randomization. In the first 24 hours, 59% of

Supervising Editor: Robert Levine, MD

patients in the restrictive fluid group received vasopressors compared with 37% in the liberal fluid group. Additionally, the liberal fluid group required vasopressors for a significantly shorter duration (mean ± SD, 5.4 ± 8.6 hours) compared with the restrictive fluid group (mean ± SD, 9.6 hours ± 10.0 hours), with a mean difference of 4.2 hours (95% CI, 3.3-5.2).[4] Thus, not only a greater number of patients in the restrictive group were admitted to the ICU, but this group also exhibited a higher frequency and longer dependence on vasopressors, leading to increased health care resource utilization.

The suggested approach of using 4 mL/kg of crystalloid fluid for resuscitation made by Toledo-Palcios et al is drawn from a quasi-randomized approach in a population admitted to the cardiothoracic ICU prior to their cardiac surgery.[5] The study focused on determining which dose of fluid would increase the mean systemic filling pressure. Extrapolating this to an approach for sepsis-induced hypoperfusion is not appropriate as the population is vastly different.

In conclusion, we agree with Toledo-Palcios et al that a tailored approach to fluids in sepsis management is helpful, though this should be applied after the initial resuscitation phase, and methods should be used that continuously assess the patient's condition. The proposed approach of starting norepinephrine, evaluating fluid responsiveness, and then delivering 4 mL/kg of crystalloid fluid is not evidence-based, nor is it practical for busy EDs. Early norepinephrine use leads to increased ICU utilization, and in situations where ICU resources are limited, this can result in prolonged boarding in the ED. Such boarding increases the risk of adverse events, compromising patient safety and care quality. High-quality interventional trials for the volume of fluid in the initial resuscitation phase (first 3-6 hours) are lacking, though equipoise to conduct a randomized control trial in sepsis-induced hypoperfusion may be lacking. What is known suggests that withholding this amount may lead to an increased risk of adverse events and health care resource utilization.

FUNDING AND SUPPORT

This study did not receive any financial support.

CONFLICT OF INTEREST

Namita Jayaprakash: honorarium for CHEST 2023 (travel) and site PI for grants to institution: Abbott Laboratories sponsored the LANER-HF trial; NIH sponsored the AIMS trial; Biocogniv sponsored the Sepsis AI marker study.

Nima Sarani: Beckman Coulter Diagnostics: site PI: Linking novel diagnostics with data-driven clinical decision support; Prenosis: site PI: Early stratification of septic patients; consulting on the clinical utility of monocyte distribution width in the acute care setting.

Namita Jayaprakash MB BcH BAO, MRCEM[1]
Nima Sarani MD[2]
H. Bryant Nguyen MD, MS[3]
Chad Cannon MD[2]

[1]*Department of Emergency Medicine, Division of Pulmonary and Critical Care Medicine, Henry Ford Hospital, Detroit, Michigan, USA*
[2]*Department of Emergency Medicine, Kansas University Medical Center, Kansas City, Kansas, USA*
[3]*Division of Pulmonary, Critical Care, Hyperbaric, and Sleep Medicine, Loma Linda University, Loma Linda, California, USA*

CORRESPONDENCE

Namita Jayaprakash, MB BcH BAO, MRCEM, Henry Ford Health, 2799 W Grand Blvd, CFP 265, Detroit, MI 48202, USA.
Email: njayapr1@hfhs.org

Received: January 11, 2025; Accepted: January 28, 2025
https://doi.org/10.1016/j.acepjo.2025.100080

ORCID

Namita Jayaprakash MB BcH BAO, MRCEM https://orcid.org/0000-0003-4045-2936

REFERENCES

1. Toledo-Palacios HA, Pérez-Nieto OR, Reyes-Monge R, Rodríguez-Guevara I, Mark NM. Sepsis resuscitation: time to embrace a restrictive fluid strategy? *J Am Coll Emerg Physicians Open*. 2025;6(2):100040.
2. Evans L, Rhodes A, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143.
3. Kuttab HI, Lykins JD, Hughes MD, et al. Evaluation and predictors of fluid resuscitation in patients with severe sepsis and septic shock. *Crit Care Med*. 2019;47(11):1582-1590.
4. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials NetworkShapiro NI, Douglas IS, et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. *N Engl J Med*. 2023;388(6):499-510.
5. Aya HD, Rhodes A, Chis Ster I, Fletcher N, Grounds RM, Cecconi M. Hemodynamic effect of different doses of fluids for a fluid challenge: a quasi-randomized controlled study. *Crit Care Med*. 2017;45(2):e161-e168.