



The CLASSIC Trial: Restrictive vs. Liberal Fluids for Septic Shock?

Key Article

Meyhoff TS, et al. *Restriction of Intravenous Fluids in ICU Patients with Septic Shock. NEJM. 2022. Published online June 17, 2022.*

Background

- Septic shock is frequently encountered in the ED and ICU.
- IVF administration is central in the resuscitation and management of patients with septic shock.
- SSC suggests an initial volume of 30 ml/kg for patients with septic shock and those with signs of hypoperfusion. Though the recommendation was downgraded with the 2021 Update.
- However, there is no recommendation on a fluid strategy for patients who continue to have signs of hypoperfusion after the initial bolus.
- We've discussed many times on CCPEM the potential harms of large volumes of IVFs (worsening respiratory failure, worsening AKI, etc.)

Objective

- Evaluate the effects of restriction of IVFs on mortality and other outcomes in adult patients with septic shock admitted to the ICU.

Methods

- International, stratified, parallel-group, open-label, randomized clinical trial
- 31 ICUs in Denmark, Norway, Sweden, Switzerland, Italy, Czech Republic, UK, and Belgium
- Patients
 - Included
 - Adults aged 18 years or older
 - Admitted to the ICU
 - Had septic shock
 - Lactate 2 mmol/L or higher
 - Ongoing infusion of vasopressor or inotrope
 - Received at least 1 L of IVF before screening
 - Onset of shock within 12 hrs of screening
 - Excluded
 - Had septic shock for > 12 hrs of screening
 - Life-threatening hemorrhage
 - Acute burn injury that involved > 10% BSA
 - Pregnancy
- Intervention
 - Patients randomized in a 1:1 ratio to restrictive IVFs or standard IVFs
 - Treatment groups not masked for patients, clinicians, or investigators
 - Restrictive IVF Group
 - Patients were given 250-500 ml crystalloid bolus

- Median cumulative volume of all fluids given in the ICU
 - Restrictive IVF Group: 10,433 ml
 - Standard IVF Group: 12,747 ml
 - Difference of 2314 ml
- Median cumulative fluid balance
 - Restrictive IVF Group: 1645 ml
 - Standard IVF Group: 2368 ml
 - Difference of 723 ml
- Protocol violations
 - Restrictive IVF Group: 162 patients (21.5%)
 - Standard IVF Group: 101 (13%)
- Primary Outcome: 90-day mortality
 - Restrictive IVF Group: 42.3%
 - Standard IVF Group: 42.1%
 - Adjusted absolute difference 0.1%
- Secondary Outcomes
 - Serious adverse events
 - Restrictive IVF Group: 29.4%
 - Standard IVF Group: 30.8%
 - Serious adverse events after IVF administration
 - Restrictive IVF Group: 4.1%
 - Standard IVF Group: 4.1%
 - Number of days alive without life support – no change
 - Number of days alive and out of the hospital – no change

Limitations

- Unblinded trial: patients and personnel aware of group assignments
- Data regarding co-interventions and hemodynamic factors not recorded
- Patients received IVFs before enrollment
- Some protocol violations occurred
- Is powering the study to detect a 7% difference the right number?

Take Home Points

- Among adult patients in the ICU with septic shock, a restrictive IVF strategy did not improve 90-day mortality compared with standard IVF therapy.