



## 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.