
# The CLOVERS Trial – Liberal Fluids or Early Pressors for Sepsis?

**Key Article**

*Shapiro NI, et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. N Engl J Med. Published online January 21, 2023. The CLOVERS Trial. The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network.*

**Background**

- IVF administration is a central tenet to the resuscitation of patients with septic shock and sepsis-induced hypotension.
- Goal of IVF administration is to restore intravascular volume that occurs in sepsis. IVF administration can augment macrovascular and microvascular perfusion and reverse organ hypoperfusion.
- IVFs can also cause a dilutional coagulopathy, fluid overload, and organ congestion/edema.
- Vasopressors are often used in sepsis-induced hypoperfusion, but also come with the risk of tissue ischemia, increased cardiac workload, and arrhythmias.
- The administration of large amounts of IVF is common during the resuscitation phase of patients with septic shock, though this practice is based on an overall low quality of evidence.
- An alternative approach (that we've also supported on CCPEM) is the earlier initiation of vasopressors and lower IVF volumes.
- The recent CLASSIC Trial (reviewed here on CCPEM) did not show a difference in 90-day mortality in ICU patients with sepsis randomized to a restrictive or unguided fluid resuscitation strategy.

**Objective**

- The CLOVERS trial was conducted to compare the effects of a restrictive fluid strategy (with early use of pressors) to a liberal fluid strategy in the first 24 hours of resuscitation in patients with sepsis-induced hypotension.

**Methods**

- Multicenter, randomized, unblinded superiority trial
- 60 US Centers
- Patients
    - Included
        - Adults aged 18 years of age or greater
        - Suspected or confirmed infection (defined as the administration or planned administration of antibiotic agents)
        - Sepsis-induced hypotension (SBP < 100 mm Hg after the administration of greater than or equal to 1 L of IVF)
    - Excluded
        - > 4 hours since meeting the criteria for hypotension refractory to at least 1 L of IVF

        - > 24 hours since presentation to the hospital
        - Previous receipt of > 3 L of IVFs (including EMS administration)
        - Evidence of fluid overload
        - Severe volume depletion from nonsepsis causes
- Trial Procedures
    - Randomized in a 1:1 ratio
    - Restrictive Fluid Strategy
        - Prioritized vasopressors as the primary treatment for sepsis-induced hypotension
        - Rescue fluids being permitted for prespecified indications that suggested severe intravascular volume depletion
    - Liberal Fluid Strategy
        - Recommended an initial 2 L IVF infusion, followed by fluid boluses on the basis of clinical triggers (i.e., tachycardia)
        - Rescue vasopressors permitted for prespecified indications
    - Each group was followed for a period of 24 hours
    - A combination of trial team supporting the protocol and the clinical team following the protocol for 24 hours
    - Allowed the administration of pressors via a central line or peripheral line
- Primary Outcome: Death from any cause before discharge home by day 90
- Secondary Outcomes – 28-day measures
    - Days free from MV
    - Days free from RRT
    - Days free from vasopressors
    - Days out of the ICU
    - Days out of the hospital

**Results**

- Enrolled a total of 1563 patients
    - Restrictive Strategy: 782 patients
    - Liberal Strategy: 781 patients
    - Patients had similar baseline characteristics (volume of IVF, pressors) before randomization
- **Data and Safety Monitoring Board recommended halting the trial for futility at the second interim analysis**
- Protocol-Guided Treatments
    - Volume of IVFs in first 6 hours
        - Restrictive Strategy: 500 ml
        - Liberal Strategy: 2300 ml
    - Cumulative Volume of IVFs during 24 hours
        - Restrictive Strategy: 1267 ml
        - Liberal Strategy: 3500 ml
    - Total median cumulative IVF including pre-enrollment IVFs
        - Restrictive Strategy: 3300 ml
        - Liberal Strategy: 5400 ml
- Primary Outcome
    - Restrictive Strategy: 14%
    - Liberal Strategy: 14.9%

    - No statistical difference
    - No difference in prespecified subgroups
- Secondary Outcomes
    - No differences in any secondary outcome measures
- Safety Outcomes
    - Number of serious adverse events was similar in both groups
    - 500 patients received vasopressors via a peripheral IV
        - 3 extravasation events
        - All resolved without intervention

**Limitations Identified by the Authors**

- Despite high adherence, some patients in the restrictive fluid group received more IVF than was intended, while some patients assigned to the liberal fluid group received lower volumes than intended.
- There may be important subgroups of patients that may benefit from a particular strategy not assessed in this study.
- Did not test a group whereby the clinicians received no guidance on therapy.
- Protocol duration was up to 24 hours and almost exclusively enrolled patients presenting to the ED.

**Take Home Point**

- A restrictive fluid strategy with early initiation of vasopressors did not result in a lower, or higher, mortality before discharge home by day 90 in patients with sepsis-induced hypotension refractory to an initial fluid bolus.