Abstract:
Although increased fluid quantities have been linked to harm in patients in the critical care unit, intravenous fluids are advised for the treatment of patients who are in septic shock (ICU). In this international, randomised trial, patients with septic shock in the ICU who had received at least 1 litre of intravenous fluid were randomly assigned to receive restricted intravenous fluid or standard intravenous fluid therapy; patients were included if the onset of shock had occurred within 12 hours of screening. Death from any cause within 90 days of randomization was the main outcome. 1554 patients were enrolled; 770 were given the restriction fluid and 784 the regular fluid. For 1545 patients, the primary outcome data were available (99.4 percent). In the ICU, the standard-fluid group received a median of 3811 ml of intravenous fluid, whereas the restrictive-fluid group received a median of 1798 ml (interquartile range, 500 to 4366). In the ICU, 221 of the 751 patients in the restrictive-fluid group (29.4%) and 238 of the 772 patients (30.8%) experienced a major adverse event at least once (adjusted absolute difference, 1.7 percentage points; 99 percent confidence interval, 7.7 to 4.3). The percentages of days living without the use of life support and days living outside of the hospital in the two groups were comparable 90 days following randomization. Intravenous fluid restriction did not cause any fewer fatalities at 90 days among adult ICU patients with septic shock compared to conventional intravenous fluid management.

Keywords: Intravenous, ICU, septic shock
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Introduction
Within the first three hours after resuscitation, the Surviving Sepsis Campaign guidelines advise an initial fixed amount of 30mL/kg of IDEAL body weight (weak recommendation, low-quality evidence). Additionally, the Surviving Sepsis Campaign Guidelines state that there is not enough data to recommend either restrictive or liberal fluid strategies for patients with sepsis and septic shock who still exhibit signs of hypoperfusion and volume depletion after initial resuscitation during the first 24 hours of resuscitation. On the one hand, using more intravenous fluids can have negative effects (such as renal damage, respiratory failure, and an increased chance of mortality). On the other hand, might result in the under resuscitation of patients with sepsis and septic shock. After the first resuscitation
of patients with septic shock, there isn't any strong evidence that fluids are beneficial, and there is some support for being more cautious with IV fluids.

Method

In this international, randomised trial, patients with septic shock in the ICU who had received at least 1 litre of intravenous fluid were randomly assigned to receive restricted intravenous fluid or standard intravenous fluid therapy; patients were included if the onset of shock had occurred within 12 hours of screening. Death from any cause within 90 days of randomization was the main outcome.

ICU patients with septic shock were randomised to:

- IV fluids with restrictions: at least 1L (Given in 250 to 500mL boluses)
- Could only provide fluids in specific situations:
  - significant hypoperfusion
  - a plasma lactate level of less than 4 mmol/L and a blood pressure of less than 50 mmHg despite the use of a vasopressor or inotrope
  - Mottling that extends over the kneecap's edge (score >2 on a 0–5 mottling scale, with higher values suggesting a larger region of mottling)
  - Within the first two hours of randomization, urinary production was less than 0.1 mL/kg/hr.
  - liquid loss (GI or drains)

Electrolytes Versus Dehydration

- If using the enteral route is not recommended, dehydration or an electrolyte shortage may occur.
- If the enteral route is prohibited, be sure to consume 1L of fluids daily, including fluids with nutrients.
- Standard intravenous fluids: standard intravenous fluid treatment
- The amount of IV fluids had no maximum amount.
- Could only provide fluids in one of the following three situations:
  - as long as the patient's hemodynamics were better
  - To replace projected or observed losses, to remedy dehydration, or to restore electrolyte balance.
  - maintenance fluids

- Both groups were permitted to consume nourishment (enteral or parenteral), enteral/oral fluids, and fluid employed as a vehicle for the delivery of medications.
- Albumin is exclusively used after abdominal paracentesis.

Inclusion criteria

- Adults above the age of 18 are included.
- Within ICU
- Had septic shock, which is defined as having a suspected or verified infection, plasma lactate less than 2 mmol/L, receiving a continuous infusion of a vasopressor or inotropic drug, and receiving at least 1 L of IV fluids in the 24 hours before to screening.
- shock starts within a day following the viewing

Exclusion criteria

- >12 hours of septic shock
- Those who didn’t consent
- potentially fatal haemorrhage
- Acute burns covering more than 10% of the body's surface area
- Pregnant or lactating females

Outcomes:

- Primary: Death within 90 days after the randomization from any reason
• Serious adverse effects are secondary (Cerebral, cardiac, intestinal, or limb ischemic events OR a new episode of severe kidney injury)
• Days without the need of invasive mechanical breathing, circulatory support, or renal replacement treatment at 90d
• Days out of the hospital and still alive at 90d

Results
1554 patients were enrolled; 770 were given the restriction fluid and 784 the regular fluid. For 1545 patients, the primary outcome data were available (99.4 percent). In the ICU, the standard-fluid group received a median of 3811 ml of intravenous fluid, whereas the restrictive-fluid group received a median of 1798 ml (interquartile range, 500 to 4366). (interquartile range, 1861 to 6762). At 90 days, the restrictive-fluid group had experienced mortality in 323 of 764 patients (42.3%) while the standard-fluid group had experienced death in 329 of 781 patients (42.1%) (adjusted absolute difference, 0.1 percentage points; 95 percent confidence interval [CI], 4.7 to 4.9; P=0.96).

In the ICU, 221 of the 751 patients in the restrictive-fluid group (29.4%) and 238 of the 772 patients (30.8%) experienced a major adverse event at least once (adjusted absolute difference, 1.7 percentage points; 99 percent confidence interval, 7.7 to 4.3). The percentages of days living without the use of life support and days living outside of the hospital in the two groups were comparable 90 days following randomization.

Summary of results:
- Enrolled 1554 patients.
- Data were available for the main outcome for 1545 (99.4%) of the patients who were recruited.
- 70 years old on average
- Average time from ICU admission to randomization: 3 hours
- Mortality in the median anticipated 90-day period: 40%
- Prehospital or ED admissions: 39%
- GI (37%) pulmonary (27%) and urinary (urine) systems were the main sites of infection (16 percent)
- 24 hours before randomization, the median IV fluid volume was about 3100 mL.
- Systemic glucocorticoid usage: 28%
- Use of respiratory assistance: 50%
- Median Fluids Received (excluding fluids given along with medications and food):
  - IV fluids with restrictions: 1798 mL (Range: 500 to 4366mL)
  - Typical IV fluids: 3811 mL (Range: 1861 to 6762mL)
- Fluids given in the ICU: Median Cumulative Volume:-
10,433 mL is the maximum amount of restricted IV fluid.

IV fluid dosage: 12,747 mL

**Death within 90d of Randomization (Primary Outcome):**

- Restricted IV Fluids: 42.3%
- Standard IV Fluids: 42.1%
- Adjusted Absolute Difference: 0.1%; 95% CI 0.4.7 to 4.9; p = 0.96
- Findings consistent after risk factors at baseline adjustment, per-protocol analysis (This is important due to the imbalance in protocol violations), and predefined subgroup analyses

**Serious Adverse Events:**

- Restricted IV Fluids: 29.4%
- Standard IV Fluids: 30.8%
- Adjusted Absolute Difference: -1.7%; 99% CI -7.7 to 4.3; p = 0.46

At 90d after randomization number of days alive without life support and days alive and out of the hospital were similar in the two groups

**Strengths:**

- Poses a therapeutically pertinent query on a prevalent clinical manifestation with previously available data of low quality.
- Expanding external validity through global and multicenter participation
- Groups were evenly distributed in terms of age, sex, comorbidities, time to randomization, source of ICU admission, focus of infection, body weight, blood values, and interventions.

- Source control, appropriate antibiotics, and norepinephrine in both groups
- Little loss in following up (0.6 percent)

**Limitations:**

Treatment groups were not blinded to participants, doctors, or researchers; nevertheless, an objective outcome lessens this.

21.5 percent of patients in the restrictive-fluid group and 13.1 percent of patients in the standard-fluid group breached the IV fluid protocol (i.e. a restrictive strategy, could be more labour intensive)

Compared to lung or urinary infections, the most prevalent infection cause was gastrointestinal (i.e. may have increased need for larger volumes of fluid replacement)

Patients received fluids prior to enrollment, there were protocol breaches, and the majority of fluids were administered outside of the protocol’s recommended quantities.

Hemodynamic parameters are not mentioned in this study (i.e. MAP). Knowing whether or not there was a difference between the groups would be helpful.

**Discussion**

The two stages of resuscitation must be understood:

- within three hours, an initial 30cc/kg of IV crystalloid (NOT ANSWERED BY THIS TRIAL)

Following the initial resuscitation, ongoing resuscitation

The second part of this construct is being attempted to be answered by this trial.
Despite the 2L intravenous fluid volume disparity between groups, ICU patients with septic shock did not have significantly different 90-day mortality or major adverse events.

After 5 days, there was hardly any difference between the groups in terms of fluids administered (1500cc) poses a significant query. Was the standard care group already receiving limited treatment, making it unable to detect a 7 percent difference? Furthermore, after 5 days, the difference in cumulative fluid balance (750mL) was likewise fairly minimal.

It's notable that the study's primary focus of infection was the gastrointestinal tract because lung infections often predominate in sepsis studies. As authors we have speculated that COVID-19’s use of treatments to minimise the transmission of airborne/aerosols (such as masks, improved ventilation, distance, staying inside, etc.) may have contributed to the reduced rate of pulmonary infections observed there compared to previous sepsis studies.

There were no statistically significant differences between the groups in the subgroup analyses, however there are two groups to be aware of since there were numerical tendencies favouring a restrictive fluid strategy. Need mechanical ventilation (My hypothesis: developing ARDS)

Initial fluid administration greater than 30 mL/kg (in my opinion, no longer fluid sensitive)

Conclusion: “Among adult patients with septic shock in the ICU, intravenous fluid restriction did not result in fewer deaths at 90 days than standard intravenous fluid therapy.”

Clinical Take Home Point: In critically ill adult patients with septic shock who received their initial 30cc/kg fluid resuscitation there are two ways to look at ongoing resuscitation based on this trial:

Restrictive fluid strategy ≠ fewer deaths at 90 days than standard fluid therapy

Restrictive fluid strategy is not worse than standard fluid therapy in terms of fewer deaths at 90 days (i.e. Safe but not superior to a standard fluid strategy)

A major caveat however is the between group differences of overall fluids given at 5 days (=1500cc) and the rather small difference in fluid balance between groups (=750cc) has to make one wonder how much standard care has changed to more of a conservative strategy overall in terms of fluid balance.

References:

1. Meyhoff TS et al. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. NEJM 2022. PMID: 35709019 [Access on Read by QxMD]

2. Evans L et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic
