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A multicenter, randomized feasibility analysis comparing restrictive fluids to standard therapy for people with sepsis in the emergency department (REFACED)

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Abstract

Aim: Sepsis presents a problem for fluid management, and clinical consensus exists about intravenous (IV) volume requirements. When adult patients with sepsis who were not in shock presented to the emergency room, our goal was to assess if a 24-hour strategy restricting IV fluid was possible (ED).

Methods: The REFACED Sepsis trial is an investigator-initiated, multicenter, randomised, open-label, feasibility study in which sepsis patients who are not in shock are randomly assigned to receive either conventional therapy or 24 hours of restrictive, crystal IV fluid delivery. Fluid boluses were only allowed in the IV fluid restriction group when certain conditions for hypoperfusion were met. The treating team determined the standard of care. Total IV crystalloid fluid volumes were the main result 24 hours after randomization. Total fluid volumes, feasibility tests, and patient-centered outcomes were also considered secondary outcomes.

Results: In the initial analysis, we included 123 patients (61 patients under restrictive care and 62 patients under normal treatment). The proportion of eligible patients who met all inclusion criteria and no exclusion criteria was 32% (95% confidence interval [CI] 28%-37%). At 24hrs, the restriction versus standard care groups had mean (± SD) IV crystalloid fluid amounts of 562 (1076) ml and 1370 (1438) ml, respectively (mean difference -801 ml, 95% CI - 1257 to - 345 ml, p = 0.001). In the fluid-restrictive group, 21 (34%) of the patients experienced protocol violations. Adverse events, the need for mechanical breathing or vasopressors, acute renal failure, length of stay, or mortality did not differ across groups.

Conclusions: In comparison to normal care, a regimen restricting IV crystalloid fluids in ED patients with sepsis resulted in lower 24-hour fluid amounts. It is possible that a future experiment may focus on patient-centered outcomes.

Keywords: Multicenter; Randomized feasibility analysis; People; REFACED

1. Introduction

Source control, supportive care, and intravenous (IV) antibiotics and fluids are all used in the treatment of sepsis. 5 The impact of IV fluids on sepsis is controversial; stringent fluid restriction may impede circulation and perfusion, whereas liberal delivery may result in fluid overload and edoema and capillary leakage. Both too little and too much fluid have also been linked to organ failure. 6-17 Despite the fact that sepsis without hypotension is more frequent than sepsis-associated hypotension and septic shock3, the Surviving Sepsis Campaign (SSC) only suggests giving 30 ml/kg of fluid within the first 3 hours for the treatment of the latter diseases. 5 The quality of the evidence used to support this advice is, however, of low quality, and better evidence has been requested. 4, 9, 18-23. In the intensive care unit (ICU), recent

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observational studies and interventional trials examining fluid amounts in adult patients with mainly septic shock have either found no difference or suggested a benefit with fluid restriction. Without a clear reason, giving 7, 24, or more IV fluids could be dangerous. 25 Patients in the intervention group who got prompt, vigorous fluid therapy had a higher mortality rate in two ED-based trials conducted in patients with sepsis and sepsis-associated hypotension in Africa. 26, 27 It is unknown if these findings apply to ED sepsis patients without shock. There do not appear to be any studies on fluid administration in patients with early sepsis who do not have shock or hypotension, despite the fact that trials are now investigating fluid regimens in patients with hypotension and septic shock28–30. The Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients (REFACED Sepsis) feasibility trial sought to determine whether a restrictive IV fluid protocol in ED patients with sepsis without shock is feasible and whether it might result in a reduction in the volume of IV fluids administered compared with standard care.

2. Material and methods

2.1. Registration and Protocol for Trials

The REFACED Sepsis trial was listed on ClinicalTrials.gov and the EU Clinical Trials Register (EudraCT number 2023-000254-55 [January 3, 2023]). The Committee on Health Research Ethics— Health Ministry Ukraine, Kyiv District accepted the research protocol. The protocol is offered as a supplement to this paper and was previously published 31.

2.2. Trial Setup and Design

A 24-hour restriction fluid delivery protocol or conventional treatment was given to patients with sepsis without shock in the REFACED Sepsis experiment, which was an investigator-initiated, multicenter, randomised, parallel-group, open-label, feasibility trial. Participants were gathered from the emergency departments of the Regional Hospital Luhansk, Poltava, and the Kyiv District Hospital. The three EDs provide 24-hour emergency care to all adult acute patients, with the exception of those who are moved immediately to catheterization laboratories, cardiology wards, stroke units, and women who are in labour. The three EDs serve a mixed rural-urban population of 0.9 million people. Patients are either admitted by ambulance following an emergency call or are referred by a general practitioner. Patient contacts range from 15,000 to 63,000 per year in the three EDs.

2.3. Selection of Participants

Patients who met each of the following inclusion requirements were included: Sepsis is defined as

- Infection suspected by the treating clinician,
- Blood cultures drawn,
- Iv antibiotics administered or planned, and
- An infection-related increase in the sofa score ≥ 232; and
- Expected hospital stay > 24 h as determined by the treating clinician.

The following criteria must be met:

- Unplanned ED admission;
- Age ≥ 18;
- Sepsis; and
- Expected hospital stay > 24 h.

Patients who met any of the following criteria were disqualified: Patients who:

- Received less than ≥ 500 ml of IV fluids;
- Had invasive ventilation or vasopressors started prior to screening;
- Had known or suspected severe bleeding as determined by the treating clinician;
- Were known or suspected to be pregnant;
- Had previously participated in the trial; or
- Were predicted by the treating clinician not to survive the following 24 hours, when submitting laboratory values during the randomization procedure on the randomization website, the SOFA score was automatically generated.

Without waiting for all laboratory results to be available for a total SOFA score at enrolment, a patient might be randomised as soon as the infection-related SOFA score was 2. With the exception of an arterial blood gas analysis, all laboratory blood tests were completed before to enrolment, the findings were accessible within a maximum of 2 hours, and a total SOFA score was generated post hoc using these results. The respiratory component of the SOFA score was taken as normal, r 0 points, in the absence of an arterial blood gas analysis. Organ dysfunction that was well known was taken into account, as stated in SEPSIS-3.32.

The lead investigator could be reached by phone 24 hours a day if there was any doubt regarding the effects of known organ malfunction. Regarding exclusion criteria (1) and (2), we presumptively did not consider patients to be in septic shock if they had not received 500 ml of IV fluids or vasopressors at the time of admission. According to Ukrainian law, people with acute illnesses may only be included in a trial if everyone involved can give written, informed consent; if no one can, a combination is not permitted. We only included patients who were unable to give written, informed permission because most sepsis patients are unable to do so. As a result, patients who appeared to be in no obvious distress and were completely alert, oriented, and/or awake. Prior to enrollment, an independent doctor gave his or her approval for inclusion. This was followed by approval from a patient's next of kin or by the patient themselves as soon as feasible after regainin0g the ability to do so.

2.4. Randomization

Patients who met all inclusion criteria and none of the exclusion criteria were randomly allocated to one of the two intervention groups in a ratio of 1:1. Site stratification was used in the randomization. In accordance with a computer-generated allocation sequence list with different block sizes (4, 6, or 8), stratified by site, randomization was carried out utilising a centralized Web-based system. Only the data manager as Trial Partner Lugansk State Medical University, who was not otherwise involved in the trial, was aware of the allocation sequence list and block sizes.

2.5. Intervention

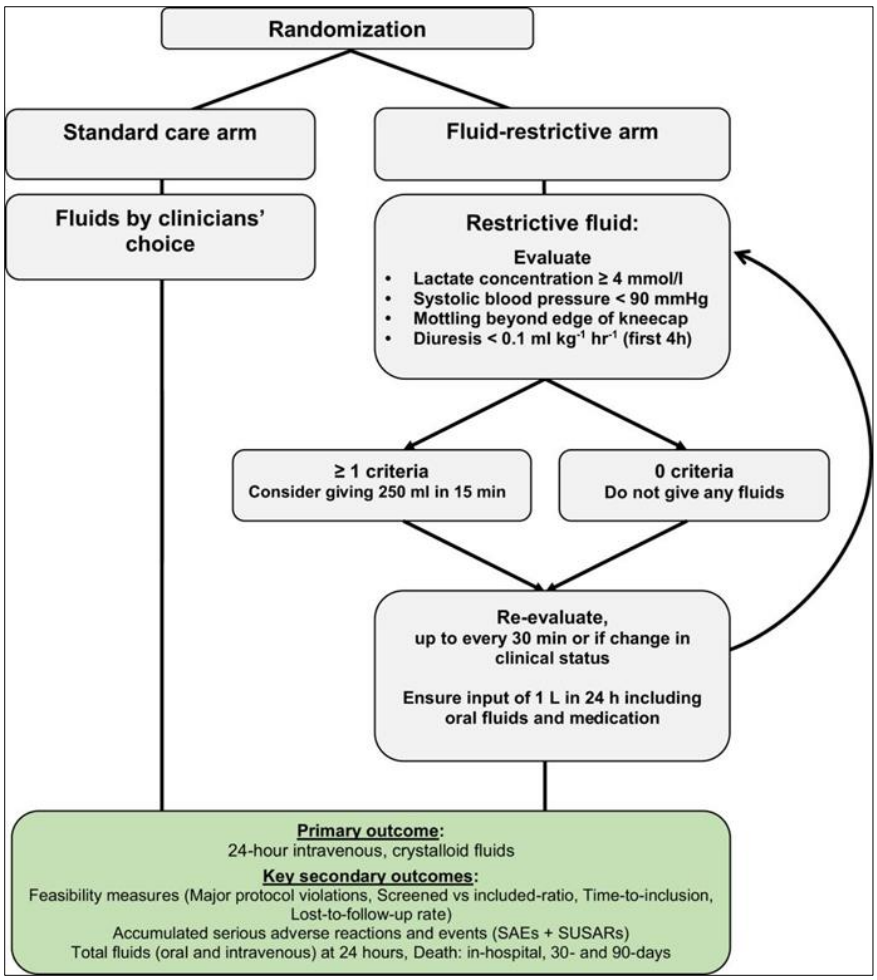

Figure 1 Treatment Algorithms: Summary of Trial Interventions

Patients received either normal care for 24 hours or restricted IV fluid administration. If the patient was transferred within the allotted 24-hour period, the prescribed treatment protocol was followed in the ED as well as the wards or ICUs. The intervention protocol focused on giving IV crystalloid fluids. Figure 1 gives a summary of the trial, including the restrictive fluid strategy.

IV crystalloid fluids should not be administered to patients in the restriction fluid group unless one of the hypoperfusion criteria listed below was satisfied:

- Lactate concentration (arterial or venous) ≥ 4 mmoL/L.
- Hypotension (systolic pressure less than< 90 mm Hg).
- Motling that extends past the kneecap's edge (i.e., Motling score > 2)33.
- Severe Oliguria, or a Diuresis rate of less than < 0.1 ml/kg/h during the first 4 hours after admission.

A fluid bolus of 250 ml of isotonic crystalloid (isotonic saline or Ringer's acetate/lactate) might be given per protocol if one or more of these conditions were true. The administration of a fluid bolus was not necessary. The treating doctor has the right to deviate from the plan at any moment by administering more fluid if they feel it is required. The doctor was required to explain why the protocol was broken. It is possible to administer drugs via IV fluids, but the volume should be minimized. If there has been a clear loss of fluid (such as through vomiting, big aspirates, diarrhoea, drain losses, or ascites drainage), IV fluid may be administered to make up the difference. If the clinical team determined that administering water or electrolyte solutions orally or intravenously was unsafe or ineffective, IV fluids could be administered to correct severe electrolyte deficiency or to guarantee a total fluid intake of 1 L per 24 hours (counting all fluids including medications and nutrition). The protocol was temporarily suspended if a patient underwent surgery during the 24-hour inclusion period, but doctors were urged to maintain restricting fluid therapy, and all intraoperative fluids were registered. Fluids were given in the standard care group at the discretion of the doctors. All patient care management, with the exception of fluid delivery, was left up to the treating team's judgement. Patients in both groups were free to consume as much alcohol as they wished or that the medical staff deemed appropriate. Blinding the intervention was not possible for the medical staff, patients, or relatives.

2.6. Measurements

The treating team, with assistance from research assistants, recorded oral and IV fluids for 24 hours in both trial groups on paper case report forms (Figures S1 and S2). The research team pulled information on baseline features, vital signs, blood tests, use of vasopressors, mechanical ventilation and dialysis, in-hospital course, and death from the electronic medical record and placed it into an electronic case report form in REDCap.

2.7. Outcomes

The total amount of intravenous crystalloid fluids given within the first 24 hours following randomization was the main outcome. The secondary outcomes included feasibility measures (number of patients randomised vs. screened positive, that is, with all inclusion criteria met and no exclusion criteria met), the amount of time it took from admission to inclusion, the number of patients who violated major protocol requirements, the number of patients whose data on the primary outcome were incomplete (for example, because they were discharged or died within 24 hours), serious adverse reactions and events within 7 days, and the total amount of fluid consumed (oral, intravenous, and combined).hospital length of stay; and in-hospital, 30-day, and 90-day mortality.

2.8. Sample Size

The sample size calculation was based on data from an observational study conducted in the Central Denmark Region in which sepsis patients meeting inclusion criteria for the current trial received a mean (±SD) of 2670 (±1695) ml IV fluids in 24 h from admission.4 We therefore estimated that the mean (±SD) total amount of crystalloid IV fluid in the standard care group would be 2650 (±1700) ml. We considered a mean (±SD) difference of 1 L to be of clinical relevance and therefore estimated 1650 (±1700) ml in the restrictive fluid group. Based on these estimates, an alpha of 5%, a power of 90%, and a two-sample t-test, a sample size of 124 patients was required.

2.9. Data Analysis

All analyses were performed on a modified intention-to-treat population, which was comprised of all randomised patients whose permission was received to use their data. Descriptive statistics were used to compare baseline characteristics. To calculate the average difference in IV crystalloid fluid volume between the assigned groups and control for the stratification variable location, we utilised linear regression. We conducted an additional post hoc analysis using median regression to calculate the difference in medians because the data were not normally distributed.

35 The analysis of other continuous variables was similar. We employed logistic regression with site-adjusted differences between groups expressed as odds ratios for binary outcomes (ORs). We used summary statistics for the feasibility measures. We performed all analyses using Stata version 17 (StataCorp LP) and considered p-values of <0.05 as statistically significant.

3. Results

3.1. Characteristics of Trial Participants

We evaluated 2412 distinct patients with probable infections between November 3, 2021, and December 18, 2021. A total of 124 individuals were randomly assigned, resulting in 62 patients being assigned to the fluid restriction group and 62 patients being assigned to the conventional treatment group. Of these, 383 distinct patients met all inclusion criteria and no exclusion criteria (Figure 2, Table S1). We analysed data from 123 patients (99%) because one patient in the restriction group withdrew consent for the use of the data. Unintentionally, one patient was included twice. The analyses took into account both admissions.

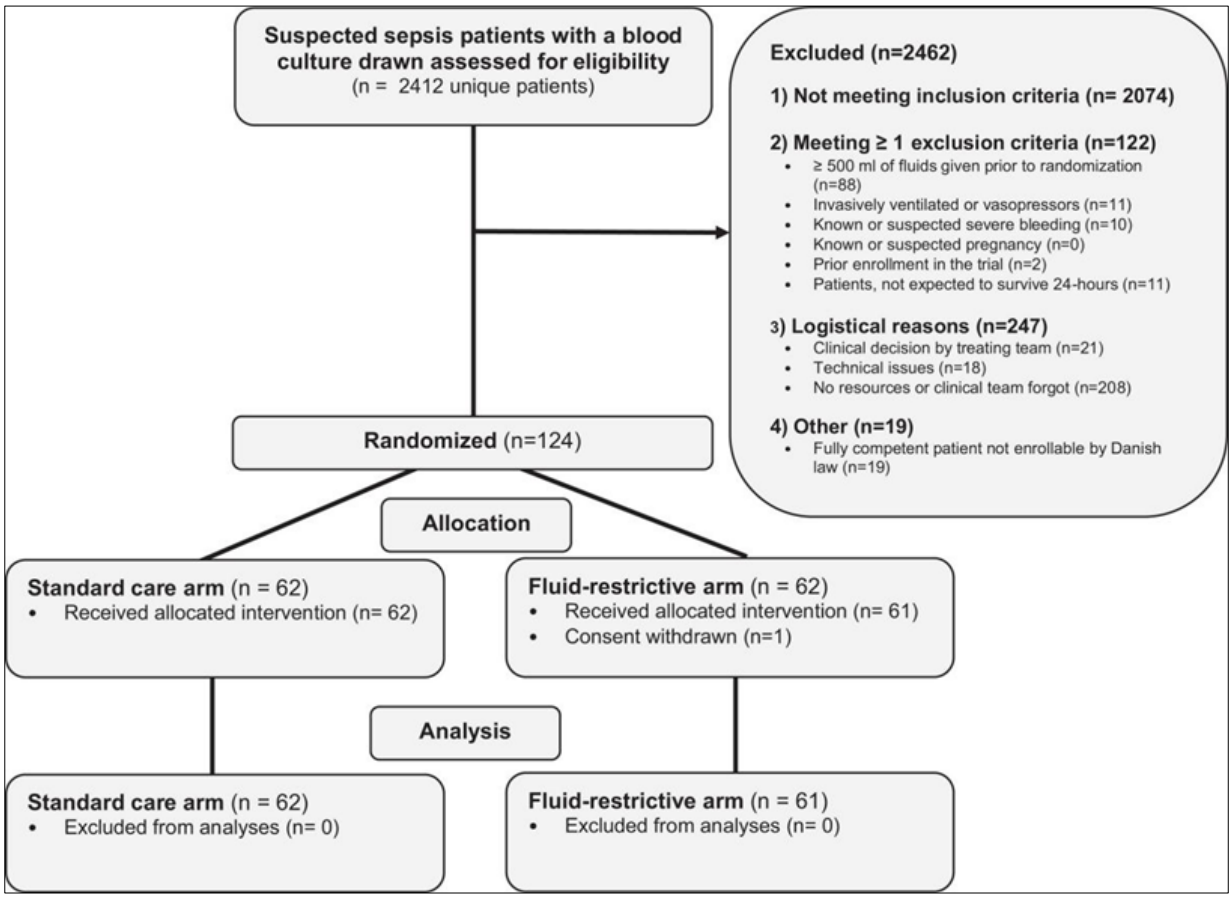

Figure 2 Screening, randomization, and follow-up in the REFACED Sepsis feasibility trial. REFACED Sepsis, Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients

Patient characteristics are presented in Table 1 and Table S1. Overall, patients had a median (IQR) age of 76 (67–84) years and 58% were male. Most patients had not received IV fluids before randomization (Table 1).

Table 1 Baseline characteristics according to group allocation

Variable	Restrictive fluids (n = 61)	Standard care (n = 62)
Age (years)	75 (67–85)	76 (68–83)
Male sex	37 (61)	34 (55)
Weight (kg)	75 (64–92)	77 (69–90)
Prior history of comorbidities		
Kidney failurea	5 (8)	9 (15)
Diabetesb	11 (18)	9 (15)
Heart failurec	9 (15)	13 (21)
DNI/DNARd	29 (48)	18 (29)
Vital signs at randomization		
Systolic blood pressure (mm Hg)	130 (107–144)	137 (126–147)
Diastolic blood pressure (mm Hg)	72 (62–79)	71 (62–83)
Mean arterial pressure (mm Hg)	88 (81–101)	94 (85–103)
Respiratory rate (breaths/min)	24 (20–28)	23 (20–28)
Oxygen saturation (%)	94 (91–96)	96 (93–97)
Heart rate (beats/min)	97 (80–115)	96 (88–110)
Temperature (°C)	38.1 (37.5–38.8)	38.6 (37.9–39.3)
GCS score	15 (15–15)	15 (15–15)
Blood tests before randomization		
Creatinine (µmol/L)	93 (65–136)	91 (65–132)
Platelet count (×109/L)	247 (179–299)	230 (157–323)
Bilirubin (µmol/L)	11 (7–21)	12 (8–18)
Leukocytes (×109/L)	14.2 (10.7–17.4)	13.5 (9.6:17.9)
C-reactive protein (mg/L)	117 (47–194)	125 (55–235)
Lactate (mmol/L)	1.2 (1.0–1.8)	1.4 (1.0–2.1)
Total SOFA score at randomizatione	3 (2–3)	3 (2–3)
Suspected infectious sourcef		
Respiratory [n with COVID-19]	45 (74) [4]	43 (69) [3]
Urinary	9 (15)	12 (19)
Skin/soft tissue	3 (5)	1 (2)
Abdominal	3 (5)	5 (8)
Other/unknown	3 (5)	4 (6)
Time to IV antibiotics from admission (h)	2.8 (1.6–3.9)	2.9 (1.6–3.9)
IV fluids given prior to randomization (ml)	0 [0–200]	0 [0–100]

Note: All data are presented as median (IQR) or n (%) unless otherwise stated; Abbreviations: DNI/DNAR, do not intubate or do not attempt resuscitation orders; GCS, Glasgow Coma Scale; a Renal failure defined according to KDIGO criteria (see supplemental material); b Diabetes requiring chronic oral or injection treatment; c Heart failure with history of ejection fraction ≤ 40%; d DNI and/or DNAR documented prior to or within 6 h of admission; e For SOFA sub-scores, see Table S1; f Some patients had more than one infectious source, why the total sum is >100%.

3.2. Feasibility Measures

Table 2 presents feasibility measures. Patients who met all inclusion criteria and none of the exclusion criteria were included in 32% (95% CI 28% to 37%) of the total patients (Regional Hospital Kyiv 43%, Lugansk State Medical University Hospital 41%, and Regional Hospital Poltava 17% [Table S2]). At admission, the characteristics of randomised patients and non randomized patients were similar, but non randomized patients more frequently reported stomach issues while randomised patients more frequently reported respiratory complaints (Table S3). From ED admission to randomization, there was a 140 (90-194) minute median (IQR) delay. Within 24 hours, five patients were discharged and one patient eventually died.

Table 2 Feasibility measures and secondary effect parameters stratified by group allocation

	Restrictive fluids (n = 61)	**Standard care (n = 62)**	**Overall (n = 123)**
Screened eligible/included ratio (%)	—	—	124/383 = 32% (95% CI 28%–37%)a
Time from ED admission to inclusion (min)			
Mean (±SD)	149 (±76)	161 (±106)	155 (±92)
Median (IQR)	140 (90–197)	139 (92–179)	140 (90–194)
Patients with incomplete data on primary outcome	2 (3)	4 (7)	6 (5)
Reasons for lost to follow-up within 24 h	1 discharge 1 death	4 discharges	5 discharges 1 death
Patients with protocol violations	21 (34)b	—	—
Patients who received no crystalloid fluid within 24 h of enrollment	38 (62)	15 (24)	53 (43)
Accumulated adverse reactions and events within 7 days	17 3 deaths, 1 myocardial infarction, 4 hypervolemia, 9 acute kidney injury	18 1 death, 1 heart failure, 2 myocardial infarctions, 4 hypervolemia, 10 acute kidney injury	35

Note: All data are presented as n (%) unless otherwise stated; a For site-specific screening/included ratio and explanations, see Table S2; b IV fluids given if none of the following was true; (a)one or more hypoperfusion criteria fulfilled; (b) to correct documented fluid loss; (c)to correct significant electrolyte deficiencies; (d) fluid administered as carrier for medication (e.g., antibiotics); (e) ensure a total fluid input of 1 L per 24 h (for the specific reasons, see Table S6).

3.3. Fluid Results

Fluid administration during the 24-h period in both groups is presented in Table 3, Figure 3, and Table S4 and S5. At 24 h, the mean (±SD) IV crystalloid volumes were 562 (±1076) ml vs. 1370 (±1438) ml in the restrictive versus standard care group and the mean (95% CI) difference was −801 ml (−1257 to −345; p = 0.001, corresponding to a relative decrease in fluid volume of 58%. The difference in medians was −1000 ml (95% CI −1392 to −607), using median regression. Thirty-eight out of 61 (62%) patients in the restrictive group and 15 of 62 (24%) patients in the standard care group received no IV crystalloid fluids in the first 24 h (Figure 3, Table S4). The mean (±SD) of combined oral and IV fluids in the first 24 h was 2881 (±1295) ml in the restrictive group versus 3720 (±1623) ml in the standard care group with a mean difference of −840 ml (95% CI −1364 to −317, p = 0.002). Further details of fluid administration, type of fluid, and time intervals are shown in Table 2, Figure 3, Tables S3–S6, and Figures S4–S7.

Table 3 Fluid volumes in the first 24 h stratified by group allocation

	Restrictive fluids (n = 61)	**Standard care (n = 62)**	**Mean difference (95% CI) or difference in medians [95% CI]a**	**p-value for mean difference**
Primary outcome				
24-h IV crystalloid fluid volumes (ml)				
Mean (±SD)	562 (±1076)	1370 (±1438)	−801 (−1257 to −345)	0.001
Median [IQR]	0 [0–600]	1000 [80–2000]	−1000 [−1392 to −607]a	
24-h IV crystalloid fluid volumes per kg bodyweight (ml/kg)				
Mean (±SD)	9 (±16)	17 (±19)	−9 (−15 to −2)	0.007
Median [IQR]	0 [0–11]	12.5 [1–26]		
Secondary outcomes				
24-h oral and IV fluid volumes (ml)				
Mean (SD)	2881 (1295)	3720 (1623)	−840 (−1364 to −317)	0.002
Median [IQR]	2820 [1900–3500]	3498 [2800 - 4450]	−660 [−1116 to −204]a	
24-h oral and IV fluid volumes per kg bodyweight (ml/kg)				
Mean (±SD)	38 (±20)	48 (±22)	−9 (−17 to −2)	0.18
Median [IQR]	36 [22–49]	45 [32–56]		
24-h other IV fluidsb (ml)				
Mean (±SD)	667 (±500)	697 (±705)	−35 (−252 to 182)	0.75
Median [IQR]	500 [400–800]	416 [300–800]		
24-h total IV fluid volume (ml)				
Mean (±SD)	1229 (±1292)	2067 (±1678)	−837 (−1374 to −298)	0.003
Median [IQR]	792 [400–1400]	1625 [1200–2650]		
24-h total oral fluid volume (ml)				
Mean (SD)	1651 (888)	1653 (816)	−4 (−310; 302)	0.98
Median [IQR]	1750 [1100–2225]	1600 [950–2150]		

Note: This table shows fluid volumes in the restrictive fluid group and in the standard care group. Mean differences and differences in medians as well as p-values are derived from the regression analyses. All mean and median differences are estimated with the standard care group as reference; a Adjusted for site. Median regression was only performed for the predefined primary and secondary outcomes.b Other IV fluids accounts for dissolved IV administered medication, glucose, plasma, albumin, blood, etc. (for further information, see Table S5).

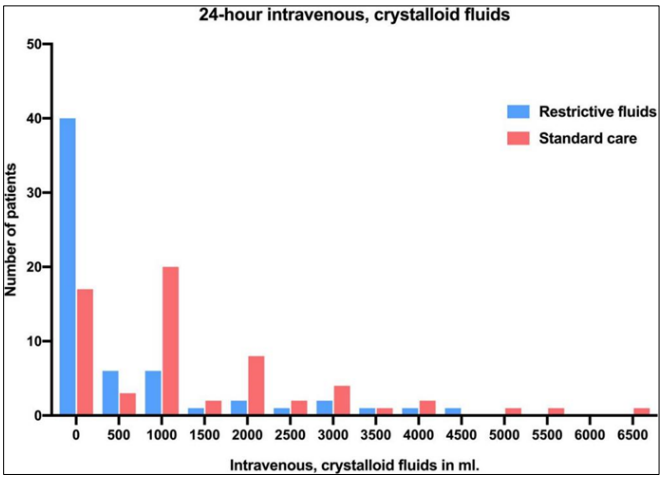

Figure 3 Distributions of 24-h IV crystalloid fluids by group allocation. Histogram showing distributions of 24-h IV, crystalloid fluids in ml by group allocation. The y-axis represents the number of patients with the given fluid volume from each group

Table 4 Reasons for fluid administration and protocol violations in the restrictive fluid group

Description of fluid indication	Number of patients with bolus/boli given for the fluid indication, N/total (%)	Number of 250 ml crystalloid boli given for the fluid indication, n
Hypoperfusion criteria		
Lactate concentration ≥ 4 mmol/La	2/61 (3.3%)	2
Hypotension (sBP < 90 mm Hg)	9/61(14.8%)	24
Mottling beyond edge of kneecapb	1/61 (1.6%)	1
Severe oliguria, i.e., diuresis < 0.1 ml/kg/hc	2/61 (3.3%)	2
Other allowed reasons for fluid administration		
Correct significant electrolyte deficiencies	3/61 (4.9%)	4
Replace fluid loss	0	0
Ensure a total fluid input of 1 L per 24 hd	0	0
Protocol violations		
Improve circulation or low blood pressure (but sBP ≥ 90 mm Hg)	5/61 (8.2%)	9
High or rising creatinine or impaired kidney function	7/61 (11.5%)	12
Dehydration indicated by treating physician	6/61 (9.8%)	9
Other reasons or administration by mistakee	12/61 (19.7%)	16

Abbreviation: sBP, systolic blood pressure; a Lactate measurement from an arterial or venous blood gas/blood sample; b Mottling score > 2 as described by Ait-Oufella et al.33; c Criteria only possible to use within first 4 h after randomization; d Total fluid input included oral fluids and fluids given with medication; e Other reasons included administering more fluid than allowed by study protocol, sparse urine output > 4 h from randomization, administration of fluid by mistake outside of protocol.

The most commonly used hypoperfusion criterion for prescribing fluids as per protocol in the restriction fluid group was hypotension. A protocol violation occurred when hydration was provided to 21 out of 61 patients despite no criteria being met. The most often cited particular justification for administering IV fluids outside of the protocol was high or

increasing creatinine/impaired renal function (Table 4). The fluid resuscitation protocol was temporarily suspended during surgery for one patient (standard care group) in accordance with the protocol, and during surgery, 2750 ml of IV fluid and medication were administered; these volumes were included in the totals but not the IV crystalloid fluid volumes.

3.4. Secondary outcomes

There were no significant differences between groups in use of mechanical ventilation or vasopressors or new-onset acute kidney failure at 7 days, nor in-hospital length of stay or in-hospital, 30-day, or 90-day mortality (Table 5).

Table 5 Secondary outcomes stratified by group allocation

Variable	**Restrictive fluids (n = 61)**	**Standard Care (n = 62)**	**Effect estimate a** **Mean difference (95% CI) and median difference [95% CI] b**	**p-value for effect estimate**
In-hospital				
length of stay (days)				
Mean (SD)	7.5 (4.9)	6.2 (5.9)	1.2 (−0.8; 3.1)	0.24 c
Median [IQR]	5.9 [4.0; 10.0]	4.9 [3.0; 7.3]	0.8 [−0.7; 2.4]	
			Odds ratio (95% CI)	
Mechanical ventilation within 7 days	2 (3.3%)	2 (3.2%)	1.01 (0.14–7.43)	0.99
Vasopressors within 7 days	2 (3.3%)	4 (6.5%)	0.49 (0.09–2.79)	0.42
New onset or worsening acute kidney failure within 7 days d	9 (14.8%)	10 (16.1%)	0.90 (0.34–2.39)	0.83
Mortality, in-hospital	7 (11.5%)	6 (9.7%)	1.19 (0.37–3.83)	0.80
Mortality, 30 days	9 (14.8%)	10 (16.1%)	0.82 (0.34–2.39)	0.83
Mortality, 90 days e	12 (19.7%)	15 (25.0%)	0.73 (0.31–1.74)	0.48

Note: All data are reported as numbers (%) if not otherwise stated; **Abbreviations**: CI, confidence interval; IQR, interquartile range; SD, standard deviation; a All analyses of effect are adjusted for site; b Median regression adjusted for site;c p value for mean difference; d Any development or worsening of acute kidney injury, defined as the KDIGO34 creatinine score >0 compared to at randomization; e Two patients withdrew consent to obtain 90-day mortality status, both from the standard care group.

3.5. Adverse Events

In the restrictive care group, there were 17 patients (28%) and 18 patients (29%) who experienced any of the specified adverse events or responses; all of these events were acute myocardial infarction, death, new-onset acute renal damage, and hypervolemia (Table 2 and Tables S7 and S8).

4. Discussion

In order to test the viability of limiting 24-hour IV crystalloid fluid amounts in sepsis patients without shock in three EDs, we conducted a randomised, multicenter experiment. The tight strategy drastically decreased the total and 24-hour IV fluid amounts. Within six weeks at three sites, we included 124 patients despite a poor randomized-to-screened ratio. Patients were randomised within a median of 140 minutes of their admission at the ED, and the majority did not receive IV fluids prior to randomization, even though randomization required taking blood cultures and findings from laboratory values prior to randomization. We believe a larger study is feasible based on these metrics of feasibility. The volume of fluid used in the trial was less than it was in the last cohort research. 4 Our sample size estimation was based on the assumption that the standard care group's total mean (SD) IV fluid consumption would be 2650 (1700) ml, as it had been for patients with similar diagnoses in our descriptive analysis. 4, 36 However, in the current experiment, the usual care group only received 2067 (1655) ml of total IV fluids. This could be a sign of the Hawthorne effect or a shift

in the way fluid administration is currently done in favour of a more restrained approach. However, there is not yet enough data to justify this practise change based on patient-centered outcomes. 28, 30, 37, 38. Contrarily, patients in the REFACED Sepsis trial received about 300 ml more oral fluids (1650 ml as opposed to 1319 ml) than in our prior descriptive study, and in general, patients received a significant amount of the total 24-hour fluids through the enteral route.

According to previous trials29, 38, and 39, the trial protocol was able to significantly lower IV fluid amounts. The median difference was 1000 ml, and the relative reduction was significant (58%), even if the mean difference (801 ml) was slightly less than the estimate we used to calculate the sample size (1000 ml). We deem a separation of 801 ml satisfactory and the protocol successful given the relatively low volume of fluid in the control group. The REFRESH study lowered 24-hour fluids from 4250 to 3543 ml in the restrictive group for ED patients with sepsis-associated hypotension, a 30% relative reduction. We nearly doubled the relative fluid volume reduction in REFACED Sepsis (58%), even though the absolute reduction in fluid amount delivered was identical between this and the current trial. The restriction group received 665 ± 1119 ml while the usual care group received 1251 ± 1588 ml, with a mean difference of 586 (62-1109) ml in the first 24 h post randomization and a relative reduction of 47%. This study, the RIFTS pilot experiment, involved ICU patients with sepsis or septic shock. 38 and the ICU-based CLASSIC septic shock feasibility experiment, despite the fact that the CLASSIC intervention lasted up to 5 days. 39. In contrast to the current trial, all of the aforementioned trials involved patients who received significant fluid volumes before to randomization, which led to total fluid intakes that were higher than ours. All three trials, however, also involved patients who were more seriously ill. The REFACED Sepsis, REFRESH, and CLASSIC trials use patient-specific hypoperfusion criteria rather than a "one-size-fits-all" approach, such as a fixed fluid amount for all patients, when deciding how much fluid to deliver. 29, 39.

The CLASSIC trials served as an inspiration for the REFACED Sepsis research and its application of hypoperfusion criteria. 28, 39 The central (systolic blood pressure), general (lactate), peripheral (mottling), and renal (oliguria) circulation and perfusion statuses were represented by the four hypoperfusion criteria. The old SSC recommendation (2016), their 1-h bundle, and data showing that the major increase in mortality occurs at lactate readings > 4 mmoL/L were used to determine the cutoff value for lactate. 42, 43 The mottling trigger was established using the Ait-Oufella et al.33 mottling score of ≥ 2 and validated in a pre hospital context. 44 While mottling might have been utilised as a marker of peripheral perfusion in recent trials,45, 46 capillary refill time was chosen because it was consistent with the CLASSIC criteria. Urine production ≤ 0.1 ml/kg/h was the criterion used to indicate severe oliguria, and it was only to be used within the first 4 hours after admission. In the 61 patients in the restrictive fluid group of the REFACED Sepsis study, a total of 29 boli of 250 ml crystalloid were administered in accordance with protocol (Table 4). In contrast to 45% and 30%, respectively, in the CLASSIC feasibility trial, the protocol was broken in 35% of the fluid-restrictive group and 24% of the patients receiving conventional care did not get IV, crystalloid fluids in 24 hours. 39 Overall, the finding that 38/61 (62%) of the patients in the restrictive group did not receive crystalloid fluids other than as a medicine carrier, to restore electrolytes, or to replace fluid loss, demonstrates that doctors can restrict fluid intake in a significant number of sepsis patients.

It's interesting to note that in the fluid-restrictive group, high or rising creatinine/impaired renal function was the most commonly cited particular justification for administering IV fluids outside the protocol. This can be the result of the widespread belief that fluid therapy should be used to treat mild pre renal kidney failure. To our knowledge, there isn't much support for this, and descriptive studies indicate that using fewer fluids can benefit health. 47-50. Our trial's advantages include the inclusion of many centres, recruitment in both university and community hospitals, and a brief inclusion time. The trial's rapid inclusion and completion emphasize its significance because sepsis patients make up a significant portion of ED patients. We think that this patient cohort, which includes elderly patients, those who are unable to give consent, and those who have high DNI/DNAR rates, constitutes a crucial patient category in emergency departments (EDs) that is typically left out of clinical trials. We view the inclusion of this patient group as a plus because it broadens the applicability of the findings.

There are a few crucial factors to take into account for a potential future large-scale experiment. It could be interesting to add patients who are a little sicker but who are still not in septic shock when they arrive, or to include more patients who have low blood pressure. It would take even closer coordination with the pre hospital services and primary in-hospital treating team to restrict IV fluid administration prior to and at arrival and thereby increase the chance of randomizing the patient because these patients frequently have fluids administered quickly pre hospital or in hospitals and thereby fulfil the exclusion criteria of receiving >500 ml before they could have possibly been included. Given the lack of data, both pre hospital and in hospitals, this may be justified.

The likelihood of discovering a difference in outcomes across treatment arms would likely increase if the sickest sepsis patients were included, but still without shock. Inclusion of additional patients with stomach infections would also boost inclusion rates and generalizability. Even stricter guidelines for fluid administration in the restrictive fluid group should be ensured, possibly focusing even more on switching from IV to oral fluid administration in this group, to ensure an even wider distinction between the groups. The duration of the intervention could also be prolonged. In the REFACED Sepsis trial, we discovered a high prevalence of DNI/DNAR orders among sepsis patients. The population was also generally older, with a median age of 76 years, and had a higher mortality rate (30-day mortality of 15%), compared to other sepsis studies, but it was similar to our descriptive study conducted before this one. 4, 29, 38, 51 There is a possibility of improving outcomes for a sizable patient population with significant mortality and high burden on healthcare systems if a relationship between fluid restriction and patient-centered outcomes, such as mortality or days alive at home, will be discovered in a future large-scale trial.

Limitations

The trial's sample size was insufficient to evaluate clinical outcomes like mortality because it was intended to demonstrate variations in IV fluid amounts. We did not establish any metrics for viability beforehand. Due to the inability to blind the allocated intervention for patients, the medical staff, or the researchers, the results may have been impacted, and fluid in the standard care group may have been more constrained than in our prior cohort trial. 4 We may have missed patients presenting with more severe sickness prehospitally or at ED admission because patients were excluded if more than 500 ml of IV fluids had been given prior to randomization. Also, patients who fulfilled all inclusion criteria later in their ED course may have been missed. Both above-mentioned limitations could affect the generalizability or the results.

Although it was similar to the mortality rates seen in a cohort analysis conducted at two of the REFACED Sepsis sites, the proportion of elderly patients and patients with DNI/DNAR prescriptions was high in the REFACED Sepsis trial, which led to a high mortality rate relative to other sepsis trials. 4 Additionally, the exclusion of 19 patients who could have given consent and were therefore ineligible for inclusion under law may have led to the inclusion of sicker individuals. Because the trial was undertaken during the COVID-19 pandemic's autumn and winter months, more patients with respiratory symptoms were probably included. Fewer patients had abdominal symptoms than in earlier studies of sepsis and fluids, which affected generalizability, at two locations because patients with a high risk of surgery within the next 24 hours were not enrolled (detailed in the supplemental material). 29, 38, 39 A low included-to-screened positive ratio was caused by these regional factors as well as COVID-19-related difficulties. Multiple departments and clinical staff were participating in this trial at the three hospitals, posing organizational difficulties and barriers. As a result, the presence of investigators, research nurses, and assistants was required to maintain the in-hospital patient flow. No differences in adverse events were seen in the two groups; however, the study was not powered to show certain differences in these.

5. Conclusion

According to the findings, it is possible to protocolize and limit 24-hour intravenous fluid amounts in EDs for sepsis patients who are not in shock. The median difference was 1000 ml, and the relative reduction was significant. The mean difference (801 ml) was somewhat less than the estimate we used to determine the sample size (1000 ml). It seems feasible to conduct a large-scale trial to examine the impact of restricting fluids on patient-centered outcomes; however, changes to the protocol may widen the IV fluid volume gap between the two intervention groups.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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