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ORIGINAL CONTRIBUTION

Restrictive fluids versus standard care in adults with sepsis in the emergency department (REFACED): A multicenter, randomized feasibility trial

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Abstract

Background: Fluid treatment in sepsis is a challenge and clinical equipoise exists regarding intravenous (IV) volumes. We aimed to determine whether a 24-h protocol restricting IV fluid was feasible in adult patients with sepsis without shock presenting to the emergency department (ED).

Methods: The REFACED Sepsis trial is an investigator-initiated, multicenter, randomized, open-label, feasibility trial, assigning sepsis patients without shock to 24 h of restrictive, crystal IV fluid administration or standard care. In the IV fluid restriction group fluid boluses were only permitted if predefined criteria for hypoperfusion occurred. Standard care was at the discretion of the treating team. The primary outcome was total IV crystalloid fluid volumes at 24 h after randomization. Secondary outcomes included total fluid volumes, feasibility measures, and patient-centered outcomes.

Results: We included 123 patients (restrictive 61 patients and standard care 62 patients) in the primary analysis. A total of 32% (95% confidence interval [CI] 28%–37%) of eligible patients meeting all inclusion criteria and no exclusion criteria were included. At 24 h, the mean (±SD) IV crystalloid fluid volumes were 562 (±1076) ml versus 1370 (±1438) ml in the restrictive versus standard care group (mean difference −801 ml,

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95% CI −1257 to −345 ml, p = 0.001). Protocol violations occurred in 21 (34%) patients in the fluid-restrictive group. There were no differences between groups in adverse events, use of mechanical ventilation or vasopressors, acute kidney failure, length of stay, or mortality.

Conclusions: A protocol restricting IV crystalloid fluids in ED patients with sepsis reduced 24-h fluid volumes compared to standard care. A future trial powered toward patient-centered outcomes appears feasible.

INTRODUCTION

Sepsis is a global health burden, estimated to cause 11 million yearly deaths. Even in survivors, sepsis can cause permanent organ dysfunction and impaired health-related quality of life.[1,2] Infections are common in emergency department (ED) patients accounting for up to one in four admissions, among these up to one in four with sepsis.[1,3,4]

The treatment of sepsis includes intravenous (IV) antibiotics and fluids, source control, and supportive care.[5] The effect of IV fluids in sepsis is debated; strict fluid restriction may lead to impaired circulation and perfusion whereas liberal administration may lead to fluid overload resulting in edema and capillary leakage, and both too little and too much has been associated with organ dysfunction.[6–17] Although sepsis without hypotension is more common than sepsis associated hypotension and septic shock,[3] the Surviving Sepsis Campaign (SSC) only gives recommendations for fluid treatment of the latter conditions with a recommendation to give 30 ml/kg within the first 3 h.[5] However, the evidence supporting this recommendation is of low quality, the use of fluid varies, and better evidence has been requested.[4,9,18–23]

Recent observational studies and interventional trials investigating fluid volumes in adult patients with primarily septic shock in the intensive care unit (ICU) have shown either no difference or indicated benefit with fluid restriction.[7,24] IV fluids given without clear indication may be harmful.[25] Two ED-based trials from Africa in patients with sepsis and sepsis-associated hypotension found a higher mortality rate among patients in the intervention group where patients received early, aggressive fluid therapy.[26,27] Whether these results are generalizable to ED sepsis patients without shock is unknown. Although trials are currently exploring fluid strategies in patients with hypotension and septic shock,[28–30] there appear to be no trials on fluid administration in patients with early sepsis without shock or hypotension.

The aim of the Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients (REFACED Sepsis) feasibility trial was to test if a restrictive IV fluid protocol in ED patients with sepsis without shock is feasible and could decrease the volume of IV fluids administered compared to standard care.

METHODS

Trial registration and protocol

The REFACED Sepsis trial was registered at the EU Clinical Trials Register (EudraCT number 2021–000224-35 [May 3, 2021]) and at ClinicalTrials.gov (identifier NCT05076435 [October 10, 2021]). The trial protocol was approved by the Committee on Health Research Ethics—Central Denmark Region (identifier 1-10-72-163-21 [June 28, 2021]). The protocol has previously been published[31] and is provided as a supplement to this paper. The trial was funded but the funding agencies had no role in the design, conduct or interpretation of the study, nor the decision to submit the manuscript for publication.

Trial design and setting

The REFACED Sepsis trial was an investigator-initiated, multicenter, randomized, parallel-group, open-label, feasibility trial, assigning patients with sepsis without shock to a 24-h restrictive fluid administration protocol or standard care. Participants were recruited in the EDs at Aarhus University Hospital, the Regional Hospital Randers, and the Regional Hospital Viborg. The three EDs serve a mixed rural–urban population of 0.9 million people and provide 24-h emergency care to all adult acute patients except those transferred directly to catheterization laboratories, cardiology wards and stroke units, and women in labor. ED patients are either referred by a general practitioner or brought in by ambulance after an emergency call. In the three EDs, patient contacts vary between 15,000 and 63,000 per year. Emergency health care in Denmark is publicly funded.

Selection of participants

We included patients fulfilling all of the following inclusion criteria: (1) unplanned ED admission; (2) age ≥ 18 years; (3) sepsis defined as (a) infection suspected by the treating clinician, (b) blood cultures drawn, (c) IV antibiotics administered or planned, and (d) an infection-related increase in the SOFA score ≥ 2[32]; and (4) expected hospital stay > 24 h as deemed by the treating clinician. We excluded patients

who fulfilled any of the following: (1) received ≥ 500 ml of IV fluids, (2) vasopressors or invasive ventilation started prior to screening, (3) known or suspected severe bleeding judged by the treating clinician, (4) known or suspected pregnancy, (5) prior enrollment in the trial, or (6) patients who the clinician expected not to survive the next 24 h. SOFA score was calculated automatically on the randomization website when entering laboratory values during the randomization process. A patient could be randomized as soon as the infection-related SOFA score was 2, without awaiting all laboratory values to be available for a total SOFA score at enrollment. All laboratory blood tests for a total SOFA score calculation—except an arterial blood gas analysis—were performed prior to enrollment, results were available within a maximum of 2 h, and a total SOFA score was calculated based on these post hoc. If an arterial blood gas analysis was not performed the respiratory component of the SOFA score was assumed normal, that is, giving 0 points. Known organ dysfunction was accounted for, as described in SEPSIS-3.[32] If there was any uncertainty about the impact of known organ dysfunction, this could be discussed with the primary investigator around the clock per telephone. Regarding exclusion criteria (1) and (2), we assumed that patients who had not received ≥500 ml of IV fluids and who had not received vasopressors at the time of inclusion were not in septic shock.

According to Danish law, patients with acute illness can only be included in a trial if all patients can provide written, informed consent *or* if none of the patients can provide written, informed consent, a combination is not possible. Since most sepsis patients are not able to provide informed consent, we only included patients who were unable to provide written, informed consent. As such, patients who were fully awake, oriented, and/or in no apparent distress were excluded.

Before enrollment, consent for inclusion was obtained from an independent physician followed by consent from a next of kin and/or the patient as soon as possible when they regained the capacity to provide consent. More details are presented in the protocol (Appendix S1).

Randomization

Eligible patients fulfilling all inclusion criteria and no exclusion criteria were randomly assigned in a 1:1 ratio to one of the two intervention groups. The randomization was stratified by site. Randomization was performed using a centralized Web-based system according to a computer-generated allocation sequence list with varying block sizes (4, 6, or 8), stratified by site. The allocation sequence list and block sizes were only known by the data manager at Trial Partner, Aarhus University, who was not otherwise involved in the trial.

Intervention

Patients were assigned to either restrictive IV fluid administration or standard care for 24 h. The assigned treatment protocol was followed in the ED as well as wards or ICUs if the patient was transferred within the 24-h period. The intervention protocol targeted IV crystalloid fluid administration. An overview of the trial, including the restrictive fluid algorithm, is provided in Figure 1.

In the restrictive fluid group, IV crystalloid fluids should not be given unless one of the below mentioned hypoperfusion criteria were met.

- Lactate concentration ≥ 4 mmoL/L (arterial or venous);
- Hypotension (systolic blood pressure < 90 mm Hg);
- Mottling beyond edge of kneecap (i.e., Mottling score > 2)[33];
- Severe oliguria, that is, diuresis < 0.1 ml/kg/h, during the first 4 h of admission.

If one or more of these criteria were met, a fluid bolus of 250 ml of isotonic crystalloid (isotonic saline or Ringer's acetate/lactate) could be administered per protocol. It was not a requirement that a fluid bolus was administered.

The treating physician could at any time violate the protocol by giving additional fluid if judged necessary. The physician had to state the reason for violating the protocol.

IV fluids could be given as carrier for medications, but the volume should be reduced if possible. In case of documented overt fluid loss (e.g., vomiting, large aspirates, diarrhea, drain losses, or ascites drainage) IV fluid could be given to correct for the loss. In case the oral/enteral route for water or electrolyte solutions was contraindicated or failed as judged by the clinical team, IV fluids could be given to correct significant electrolyte deficiencies or to ensure a total fluid input of 1 L per 24 h (counting all fluids including medications and nutrition). If a patient underwent surgery during the 24-h inclusion period, they temporarily paused the protocol, but clinicians were encouraged to continue restrictive fluid therapy, and all intraoperative fluids were registered.

In the standard care group, fluids were administered by clinicians' choice. Aside from the fluid administration, all management of the patient care was at the discretion of the treating team. In both groups, patients were allowed to drink as much as desired or allowed by the treating team. It was not possible to blind the intervention for neither the treating team, patients, nor relatives.

Measurements

In both trial groups, oral and IV fluids were registered on a paper case report form for 24 h (Figures S1 and S2) from randomization by the treating team with help from research assistants. Data were obtained from the electronic medical record by the research team on baseline characteristics, vital signs, blood tests, use of vasopressors, mechanical ventilation and dialysis, in-hospital course, and death and entered in an electronic case report form in REDCap.

Outcomes

The primary outcome was the total volume of IV crystalloid fluids administered during the first 24 h after randomization. The

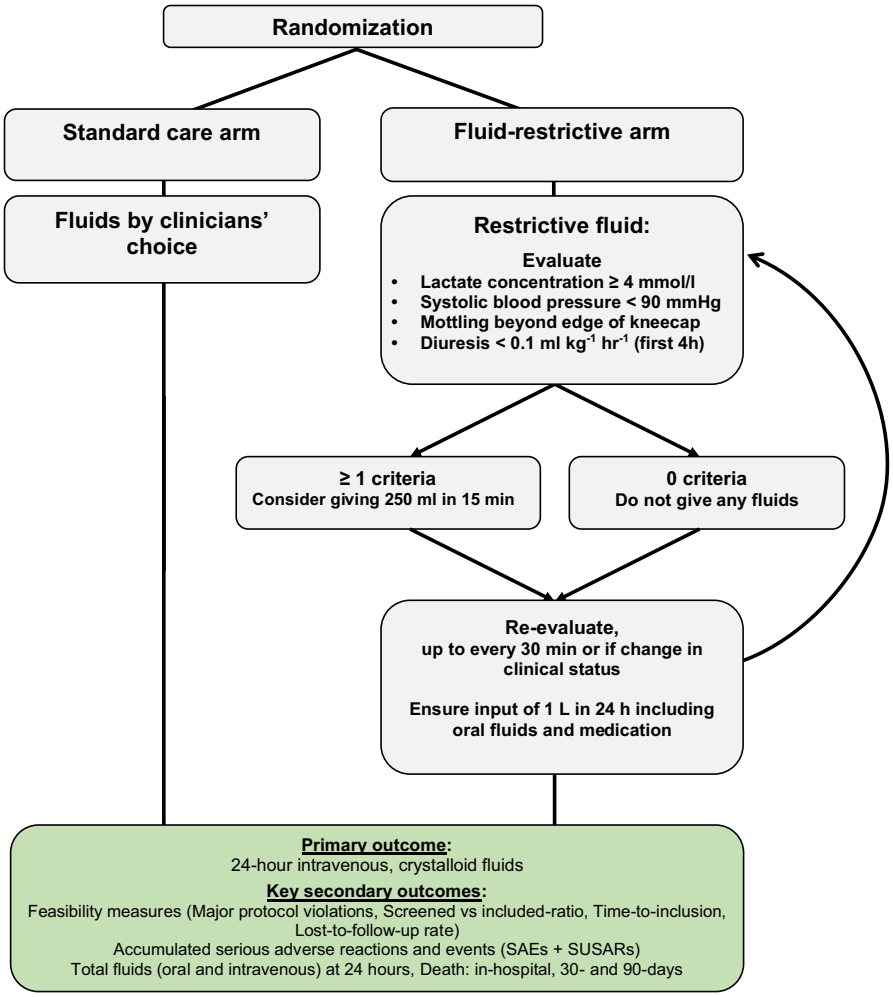

FIGURE 1 Treatment algorithms: summary of trial interventions.

secondary outcomes were feasibility measures (number of patients randomized vs. screened positive, i.e., with all inclusion criteria fulfilled and no exclusion criteria fulfilled); time from admission to inclusion; number of patients with major protocol violations; number of patients with incomplete data on the primary outcome (e.g., due to discharge or death within 24 h); serious adverse reactions and events within 7 days; total fluid volume (oral, IV, and combined) at 24 h; mechanical ventilation within 7 days; vasopressor use within 7 days; development or worsening of acute kidney failure according to the KDIGO3 criteria[34] within 7 days of randomization; hospital length of stay; and in-hospital, 30-day, and 90-day mortality.

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.

Data analysis

All analyses were conducted in a modified intention-to-treat population defined as all randomized patients for whom consent to use data was obtained. Baseline characteristics were compared using descriptive statistics. We used linear regression to estimate the mean difference in IV crystalloid fluid volume between the allocated groups with adjustment for the stratification variable site. As the data were not normally distributed, we performed an additional post hoc analysis using median regression to estimate the difference in medians.[35] Other continuous variables were analyzed similarly. For binary outcomes, we used logistic regression adjusted for site with differences between groups presented as odds ratios (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.

RESULTS

Characteristics of trial participants

From November 3, 2021, to December 18, 2021, we screened 2412 unique patients with suspected infection. Of these, 383 unique patients met all inclusion criteria and no exclusion criteria, and 124 patients were randomized (Figure 2, Table S1); 62 patients were assigned to the fluid restriction group and 62 were allocated to the standard care group. One patient in the restrictive group withdrew consent for the use of data; we thus analyzed data from 123 patients (99%). One patient was inadvertently included twice. Both admissions were included in the analyses.

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).

Feasibility measures

Feasibility measures are shown in Table 2. Overall, 32% (95% CI 28% to 37%) of patients meeting all inclusion criteria and no exclusion criteria were included (Regional Hospital Viborg 43%, Aarhus University Hospital 41%, and Regional Hospital Randers 17% [Table S2]). Randomized patients and nonrandomized patients were similar in characteristics at admission, but nonrandomized patients more often presented with abdominal complaints whereas randomized patients more of the had respiratory complaints (Table S3). The median (IQR) time from ED admission to randomization was 140 (90–194) min. One patient died and five patients were discharged within 24 h.

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

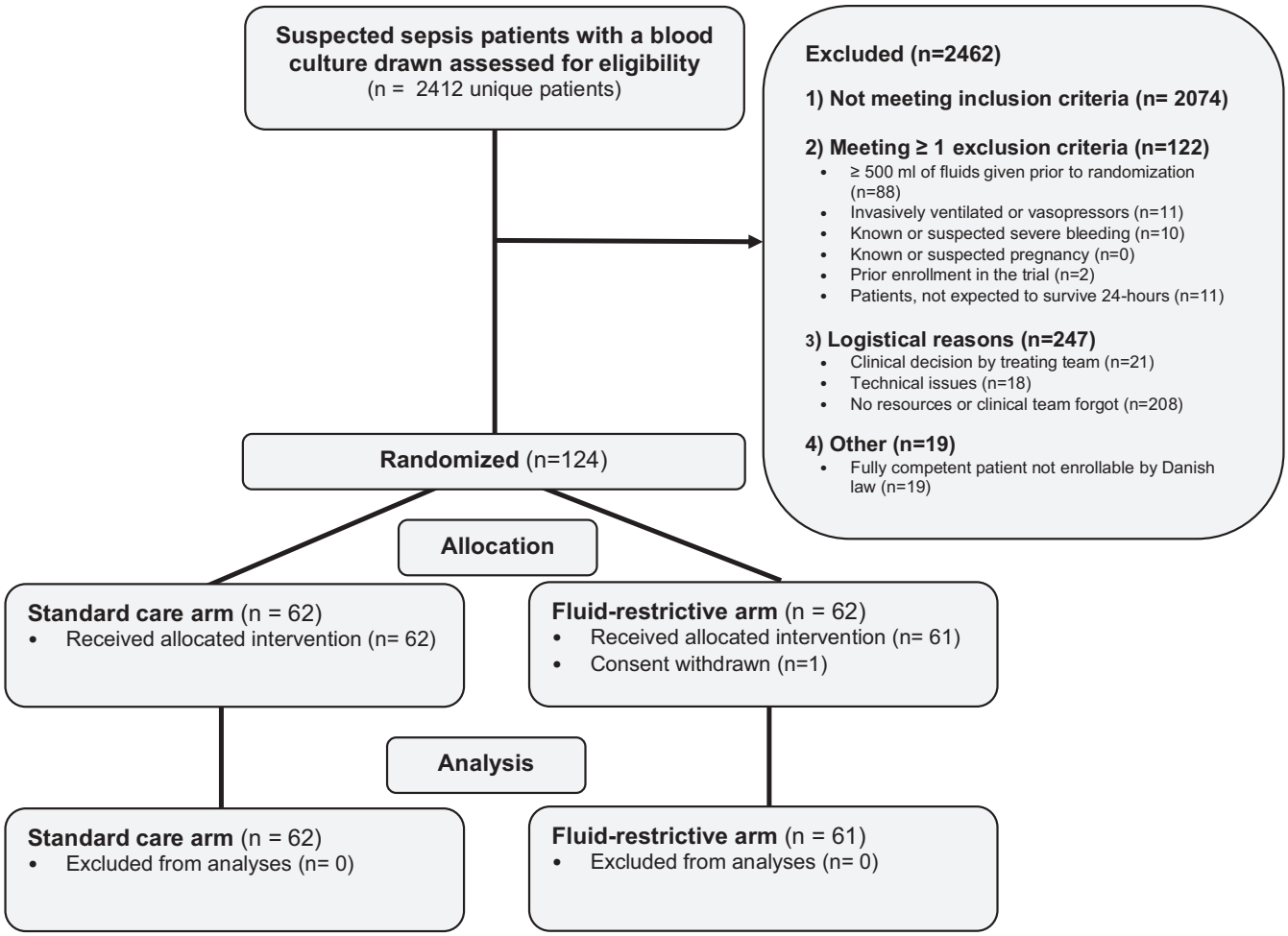

FIGURE 2 Screening, randomization, and follow-up in the REFACED Sepsis feasibility trial. REFACED Sepsis, Restrictive Fluid Administration vs. Standard of Care in Emergency Department Sepsis Patients.

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 failure[a]	5 (8)	9 (15)
Diabetes[b]	11 (18)	9 (15)
Heart failure[c]	9 (15)	13 (21)
DNI/DNAR[d]	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 ($\times 10^9$/L)	247 (179–299)	230 (157–323)
Bilirubin (μmol/L)	11 (7–21)	12 (8–18)
Leukocytes ($\times 10^9$/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 randomization[e]	3 (2–3)	3 (2–3)
Suspected infectious source[f]		
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 subscores, see Table S1.

[f]Some patients had more than one infectious source, why the total sum is >100%.

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.

In the restrictive fluid group, hypotension was the most frequently used hypoperfusion criterion for administering fluids per protocol. Twenty-one of 61 patients had fluid administered despite no criteria fulfilled, that is, had a protocol violation. High or rising creatinine/impaired renal function was the most frequently used specific reason for giving IV fluids outside the protocol (Table 4). One patient (standard care group) underwent surgery and had the fluid resuscitation protocol temporarily suspended during surgery in accordance with the protocol and had a total 2750 ml of IV fluid and medication administered during surgery, included in total volumes but not in IV crystalloid fluid volumes.

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).

Adverse events

There were 17 (28%) and 18 (29%) patients experiencing any of the predefined adverse events or reactions in the restrictive and standard care groups, respectively, with acute myocardial infarction, death, new-onset acute kidney injury, and hypervolemia accounting for all events (Table 2 and Tables S7 and S8).

DISCUSSION

We conducted a randomized, multicenter trial to examine the feasibility of restricting 24-h IV, crystalloid fluid volumes in sepsis patients without shock in three EDs. The restrictive protocol significantly reduced 24-h IV fluid volumes and total fluid volumes.

Despite a low randomized-to-screened ratio, we included 124 patients within 6 weeks at three sites. Although randomization required drawing of blood cultures and results from laboratory values prior to randomization, patients were randomized within a median of 140 min of arrival to the ED and most patients did not receive IV fluids prior to randomization. Based on these feasibility measures, we consider a larger trial feasible.

Fluid volumes in the current trial were lower than those in our previous cohort study.[4] In our sample size estimation, we assumed

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).

that the total mean (±SD) amount of IV fluid in the standard care group would be 2650 (±1700) ml as it was for similar patients in our descriptive study.[4,36] However, the standard care group only received 2067 (±1655) ml total IV fluids in the present trial. This may represent the Hawthorne effect and/or a change in current practice toward more restrictive fluid administration in general. However, there is limited evidence on patient-centered outcomes to support this change of practice yet.[28,30,37,38] On the other hand, patients in the REFACED Sepsis trial received approximately 300 ml more oral fluids than in our previous descriptive study (1650 ml compared to 1319 ml), and in general patients had a large proportion of the total 24-h fluids through the enteral route.

The trial protocol was, in line with recent trials,[29,38,39] able to substantially reduce IV fluid volumes. Although the mean difference (801 ml) was slightly lower than the estimate used in our sample size calculation (1000 ml), the median difference was 1000 ml, and the relative reduction was large (58%). Given the relative low volume of fluid in the control group, we consider a separation of 801 ml satisfactory and the protocol successful. In ED patients with sepsis-associated hypotension, the REFRESH trial reduced 24-h fluids from 4250 to 3543 ml in the restrictive group, with a relative reduction of 30%. Although the absolute reduction in fluid volume administered were similar between this and the current trial, we almost doubled the relative fluid volume reduction in REFACED Sepsis (58%). The 58% reduction is more in line with the RIFTS pilot trial, where ICU patients with sepsis or septic shock received 665 ± 1119 ml in the restrictive group and 1251 ± 1588 ml in the usual care group with a mean difference of 586 (62–1109) ml in the first 24 h postrandomization and a relative reduction of 47%[38] and the ICU-based CLASSIC septic shock feasibility trial, although the intervention in CLASSIC lasted for up to 5 days.[39] However, in all the above-mentioned trials, patients received large fluid volumes prior to randomization in opposition to this current trial resulting in total fluids exceeding our totals but all three trials were also conducted in more severely ill patients. The REFACED Sepsis, REFRESH, and CLASSIC trials use patient specific hypoperfusion criteria for administering fluid in contrary to a "one-size-fits-all" strategy for example with a fixed fluid volume for all patients.[29,39]

The REFACED Sepsis study and its use of hypoperfusion criteria was inspired by the CLASSIC trials.[28,39] The four hypoperfusion criteria were chosen to represent central (systolic blood pressure), general (lactate), peripheral (mottling), and renal (oliguria) circulation and perfusion status. The cutoff value of lactate was chosen based on the former SSC guideline (2016),[40] and their 1-h bundle[41] and

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 fluids[b] (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).

data indicating that the marked increase in mortality occur at lactate values > 4 mmoL/L.[42,43] The mottling trigger was based on mottling score of ≥2 as described by Ait-Oufella et al.[33] and validated in a pre-hospital setting.[44] Recently, some trials have used capillary refill time as a marker of peripheral perfusion,[45,46] which could have been used instead of mottling but it was chosen to align with the CLASSIC criteria. Severe oliguria was defined as urine output ≤ 0.1 ml/kg/h and the criterion was only to be used within the first 4 h of admission. In the REFACED Sepsis trial, a total of 29 boli of 250 ml crystalloid were given per protocol in the 61 patients in the restrictive fluid group (Table 4). The protocol was violated (i.e., giving fluids although no hypoperfusion criteria were fulfilled) in 35% in the fluid restrictive group and 24% did not receive IV, crystalloid fluids in 24 h in the standard care group, in comparison to 45% and 30%, respectively, in the CLASSIC feasibility trial.[39] Overall, the fact, that 38/61 (62%) patients in the restrictive group did not receive crystalloid fluids unless as carrier for medication, to correct electrolytes or to replace fluid loss, shows that clinicians are able to restrict fluids in a large proportion of sepsis patients.

Interestingly, the most frequently used specific reason for giving IV fluids outside the protocol in the fluid-restrictive group was high or rising creatinine/impaired renal function. This may be due to a general perception that a low degree of prerenal kidney failure should be treated with fluids. However, the evidence for this to our knowledge is limited, and descriptive studies show improvement with less fluids.[47–50]

The strengths of our trial include the multicenter inclusion, recruitment in both university and regional hospitals, and a short inclusion period. The fast inclusion and completion of the trial underlines the importance of the trial; sepsis patients account for a large proportion of ED patients. We believe, this patient population (i.e., older, high do not intubate/do not attempt resuscitation [DNI/

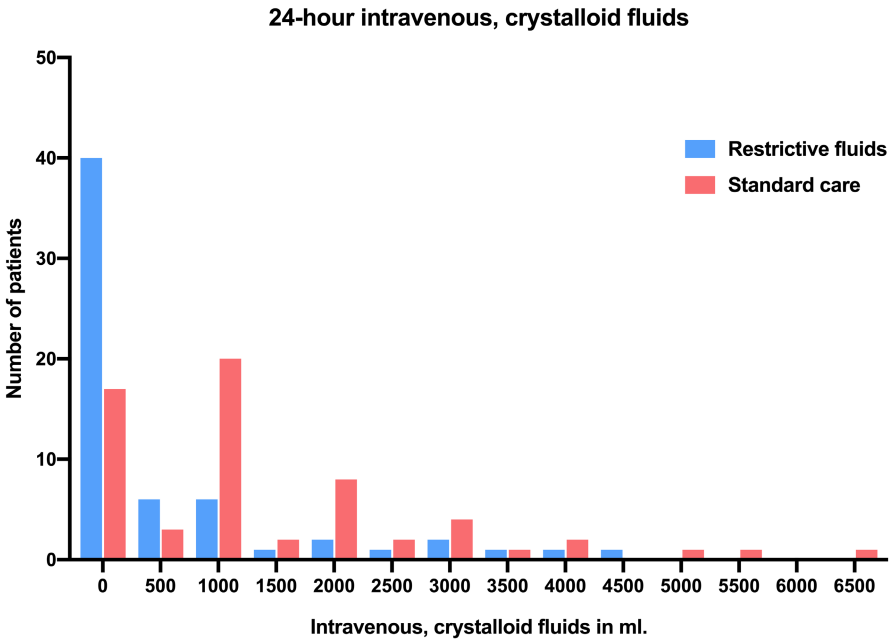

FIGURE 3 Distributions of 24-h IV crystalloid fluids by group allocation. Histogram showing distributions of 24-h IV, crystalloid fluids in ml by group allocation. The y-axis represents the number of patients with the given fluid volume from each group.

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/L[a]	2/61 (3.3%)	2
Hypotension (sBP < 90 mm Hg)	9/61(14.8%)	24
Mottling beyond edge of kneecap[b]	1/61 (1.6%)	1
Severe oliguria, i.e., diuresis < 0.1 ml/kg/h[c]	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 h[d]	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 mistake[e]	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.

DNAR] rate, unable to consent) represents a very important patient group in the ED, which have traditionally not been included in clinical trials. We consider the inclusion of this patient population a strength as it increases the generalizability of the results.

There are some important considerations for a possible future large-scale trial. It could be of interest to include patients slightly sicker but still without septic shock at arrival, that is, including more patients with low blood pressure. Since these patients often rapidly have fluids administered prehospital or in hospital and thereby fulfill the exclusion criteria of receiving >500 ml before they could possibly have been included, it would require even closer contact to the prehospital services and first-line in-hospital treating team to limit IV

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 KDIGO[34] creatinine score >0 compared to at randomization.

[e]Two patients withdrew consent to obtain 90-day mortality status, both from the standard care group.

fluid administration prior to and at arrival and thereby increase the chance of randomizing the patient. This may be appropriate since the evidence is still very sparse both prehospital and in hospital. Including the sickest sepsis patients, but still without shock, would probably increase the chance of finding a difference in outcomes between treatment arms. Also, it would increase inclusion rates and the generalizability to include more patients with abdominal infections. To ensure an even greater separation between the groups, even stricter criteria for fluid administration in the restrictive fluid group should be ensured, maybe focusing even more on changing from IV to oral fluid administration in this group. Also, the intervention period could be extended.

We found a high prevalence of DNI/DNAR orders within the sepsis population in the REFACED Sepsis trial, and the population was in general older with a median age of 76 years and a high mortality (30-day mortality of 15%) in comparison to other sepsis studies, but similar to our descriptive study leading up to this study.[4,29,38,51] If an effect of fluid restriction on patient-centered outcomes, for example, mortality or days alive at home, will be found in a future large-scale trial, there is a potential of improving outcomes for a large patient group with significant mortality and high burden on health care systems.

LIMITATIONS

The trial was designed to show differences in IV fluid volumes and the sample size was therefore inadequate to assess clinical outcomes such as mortality. We did not prespecify any benchmarks for feasibility. It was not possible to blind the allocated intervention for neither patients, the treating team, nor investigators, which may have affected the results and potentially caused fluid in the standard care group to be quite restrictive in comparison to our previous cohort study.[4] Since patients were excluded if more than 500 ml of IV fluids had been administered prior to randomization, we may have missed patients presenting with more severe illness prehospitally or at ED admission. 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.

The proportion of elderly patients, and patients with DNI/DNAR orders was high in the REFACED Sepsis trial, resulting in a high mortality rate compared to other sepsis studies, although it was similar to the ones found in a cohort study conducted at two of the sites in REFACED Sepsis.[4] Also, the fact that 19 patients were not included since they were actually able to provide consent and there for not includable due to Danish regulations may have caused inclusion of sicker patients. The trial was conducted during autumn and winter season, during the COVID-19-pandemic, which likely resulted in inclusion of more patients with respiratory symptoms. At two sites, patients with a high risk of surgery within the 24 h were not enrolled (described in supplemental material), resulting in few patients with abdominal symptoms in comparison to other trials in sepsis and fluids affecting the generalizability.[29,38,39] These local conditions, as well as challenges related to COVID-19, contributed to a low included-to-screened positive ratio. To keep the in-hospital patient flow, multiple

departments and clinical personnel were involved in this trial at the three hospitals causing organizational challenges and obstacles, and thus presence of investigators, research nurses, and assistants was necessary. No differences in adverse events were seen in the two groups; however, the study was not powered to show certain differences in these.

CONCLUSIONS

The results indicate that it is feasible to protocolize and restrict 24-h intravenous fluid volumes in sepsis patients without shock in EDs. The mean difference (801 ml) was slightly lower than the estimate used in our sample size calculation (1000 ml), but the median difference was 1000 ml, and the relative reduction was large. A large-scale trial to investigate the effect of restrictive fluids on patient-centered outcomes appears feasible; however, modifications to the protocol may increase the separation in intravenous fluid volumes between the two intervention groups.

AUTHOR CONTRIBUTIONS

Marie K. Jessen, Lars W. Andersen, Anders Perner, Jens Aage K. Petersen, and Hans Kirkegaard conceived the study and designed the trial. Marie K. Jessen and Hans Kirkegaard obtained research funding. Lars W. Andersen, Anders Perner, Jens Aage K. Petersen, and Hans Kirkegaard supervised the conduct of the trial. Marie K. Jessen, Marie-Louise H. Thomsen, Peter Kristensen, Wazhma Hayeri, Tina G. Messerschmidt, Christoffer G. Sølling, and Ranva E. Hassel undertook recruitment of patients. Peter Kristensen, Wazhma Hayeri, Christoffer G. Sølling, and Ranva E. Hassel were site investigators. Marie-Louise H. Thomsen and Marie K. Jessen collected data. Marie K. Jessen managed the data, including quality control. Lars W. Andersen provided statistical advice. Marie K. Jessen drafted the manuscript, and all authors contributed substantially to its revision. Marie K. Jessen takes responsibility for the paper as a whole.

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CONFLICT OF INTEREST

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TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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