Protocolised early de-resuscitation in septic shock (REDUCE): protocol for a randomised controlled multicentre feasibility trial

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ABSTRACT

Background Fluid overload is associated with excess mortality in septic shock. Current approaches to reduce fluid overload include restrictive administration of fluid or active removal of accumulated fluid. However, evidence on active fluid removal is scarce. The aim of this study is to assess the efficacy and feasibility of an early de-resuscitation protocol in patients with septic shock.

Methods All patients admitted to the intensive care unit (ICU) with a septic shock are screened, and eligible patients will be randomised in a 1:1 ratio to intervention or standard of care. Intervention: Fluid management will be performed according to the REDUCE protocol, where resuscitation fluid will be restricted to patients showing signs of poor tissue perfusion. After the lactate has peaked, the patient is deemed stable and assessed for active de-resuscitation (signs of fluid overload).

The primary objective of this study is the proportion of patients with a negative cumulative fluid balance at day 3 after ICU. Secondary objectives are cumulative fluid balances throughout the ICU stay, number of patients with fluid overload, feasibility and safety outcomes and patient-centred outcomes. The primary outcome will be assessed by a logistic regression model adjusting for the stratification variables (trial site and chronic renal failure) in the intention-to-treat population.

Ethics and dissemination The study was approved by the respective ethical committees (No 2020–02197). The results of the REDUCE trial will be published in an international peer-reviewed medical journal regardless of the results.

Trial registration number ClinicalTrials.gov, NCT04931485.

INTRODUCTION

Sepsis/septic shock is among the most common diagnosis for intensive care unit (ICU) admission and mortality is still substantial.1,2 The key element in the initial management of patients with septic shock are the sepsis bundles, which include initial intravenous fluids as well as the use of vasopressors, antibiotics, source control and supportive care.3,4 Patients with septic shock often receive large amounts of fluids, which results in considerable amounts of fluid overload (FO) in respective patients.5–8 In addition, capillary leakage as a result of impaired barrier function is an important contributor to FO in patients with sepsis.9 Recent data suggest that capillary leakage might even be promoted by intravenous fluid administration through amplifying endothelial dysfunction, creating a ‘vicious cycle’.9 Thus, the ‘optimal dose’ of fluids in the early phase of septic shock (resuscitation phase) has been subject to investigations and much debate.6,7,10

Current evidence suggests that FO is harmful for critically ill patients.11 So how to avoid FO in patients with sepsis/septic shock? Two strategies aiming at limiting FO and its consequences have been investigated: (1) a restrictive fluid administration or (2) active removal of accumulated fluid with diuretics or renal replacement therapy (RRT). Several small and two large multicentre studies have shown that fluid restriction in patients with septic shock is safe and feasible.12–16 While two large randomised-controlled multicentre trials indicated that fluid restriction is not
harmful, no survival benefit was detected. In contrast, trials on active protocolised de-resuscitation in patients with septic shock are scarce. Current observational evidence on fluid de-resuscitation indicates that early and targeted fluid removal might reduce net fluid balance in the critically ill patient, and is associated with improved patient outcome.

Aims and hypothesis
This study aims to assess the efficacy and feasibility of an early active de-resuscitation protocol in patients with septic shock. We hypothesise that application of a structured early de-resuscitation protocol versus standard of care will lead to less FO at intensive care discharge.

METHODS AND ANALYSIS
The REDUCE trial is an investigator-initiated, multicentre, open-labelled, randomised-controlled, stratified, outcome assessor-blinded trial. The protocol has been prepared according to the Standard Protocol Items: Recommendation for Interventional Trials statement, and the trial will adhere to the Declaration of Helsinki, as well as the national law on conducting clinical research projects. The study is a Swiss multicentre study and will be conducted at the University Hospital Bern, Inselspital, the Cantonal Hospital St. Gallen, the Cantonal Hospital Winterthu and the University Hospital Basel, Switzerland. The trial has been approved by the ethical committee (Lead EC Canton Bern, No 2020–02197). The trial has been prospectively registered on ClinicalTrials.gov. The trial started in July 2019 at the main trial site, University Hospital Bern, Switzerland. At the Canton Hospital St. Gallen, the study start is scheduled for May 2023 and for the two other centres in summer 2023. The end of the study is planned for December 2024.

Definitions
Cumulative fluid balance
Fluid balance is calculated as the difference between all cumulative fluid intakes (ie, nutrition, resuscitation fluids, maintenance fluids, drug fluids and oral fluids) and all cumulative fluid losses including urine losses, all drainage losses, faecal losses and evaporation. The data will be retrieved from the electronic patient file.

Fluid overload
We defined FO when the cumulative fluid balance is more than 5% of the baseline body weight ((cumulative fluid intake–cumulative fluid losses)/(admission weight)×100).11,25

Inclusion and exclusion criteria
Inclusion and exclusion criteria are listed in box 1. In brief, all patients admitted to ICU or transferred from another ICU with a diagnosis of septic shock as defined according to the Sepsis-3 criteria are screened for eligibility. Exclusions criteria entail age below 18 years, acute burn injury >10% of body surface area, septic shock for >12 hours at the time of screening, patient on chronic dialysis, pregnant or lactating women or allergy to diuretic agents administered, consent not obtainable due to national regulations.

Randomisation
Patients fulfilling the inclusion criteria are randomised 1:1 using a web-based system (Research Electronic Data Capture (REDCap), V12.4.12) according to a computer-generated allocation sequence list. Patients will be stratified by known pre-existing chronic kidney dysfunction (Kidney Disease Improving Global Outcomes (KDIGO) G3a or higher).27 The allocation list and block sizes are only known to the data manager at the clinical trial unit (CTU) of the University of Bern, Bern, Switzerland.

Blinding procedures
The trial will be conducted as an open-label study. All site personnel will be aware of treatment allocation. Outcome assessors will be blinded to the treatment allocation and all treatments.

The risk of bias will be minimised by using a prespecified statistical analysis plan and by measuring objective outcomes such as fluid balance, time and days on supportive treatment (RRT, mechanical ventilation, etc).

Study intervention
The active REDUCE study period is the time spent on ICU up to 7 days after randomisation or to ICU discharge. Patients will be followed up to 90 days.

REDUCE protocol group
Study interventions consist of the application of a structured fluid management protocol for patients with sepsis (see figure 1). Apart from the fluid management, all other therapies related to the management of septic shock (eg, antibiotic therapy, surgical interventions) are according
Figure 1  REDUCE fluid management protocol. ABG(A), arterial blood gas analysis; BW, body weight; GFR, glomerular filtration rate; ICU, intensive care unit; RRT, renal replacement therapy; UO, urine output; US, ultrasound; XR, x-ray.

1. Blood transfusions. Albumin for ascites according to clinical standard
2. Swutch all drugs to per oral application where possible
3. Contraindication: Peripheral artery disease, Bypass, local skin disorder
to the treating physicians and will be the same as in the control group.

The REDUCE protocol has two main parts: (A) resuscitation and (B) de-resuscitation part.

Part (A): resuscitation

No intravenous fluids will be administered unless one of the circumstances listed below is present and the patient has been clinically assessed as needing fluids:
- Capillary refill $\geq$2 s, OR
- Mottling score $\geq$2, OR
- Severe sinus tachycardia $\geq$130/ min, OR
- Lactate $\geq$4 mmol/L.

Patients fulfilling one or more of the above criteria receive a fluid bolus of 4 mL/kg BW over 30 min, as this amount has been shown to reliably detect fluid responders and non-responders. Only crystalloid fluids will be administered. All thresholds above have been chosen as they have been shown to be associated with increased mortality in the critically ill.

Overt fluid losses (eg, vomiting, large aspirates, diarrhoea, drainage losses, bleeding or ascites) can be compensated by intravenous fluid administration (maximum 1:1). If the patient’s haemoglobin level is below 70 g/L, transfusion of red blood cells can be considered. In the case of ascites drainage, albumin may be administered per 2 L of ascites removed above 2 L. Intravenous fluids may be given as drug carriers, but the amount should be reduced to the lowest possible volume for the given medication. Maintenance fluid should not be given. Enteral or parenteral nutrition as well as per oral fluid are allowed.

Part (B): de-resuscitation

Once the lactate level has peaked (decreased in two consecutive measurements), the patient transitions into the de-resuscitation phase. Negative fluid balance (current output-input) is targeted if:
- The patient has a positive cumulative fluid balance since ICU admission.
- Is at high risk of developing FO (massive blood transfusions, high volume drug therapy, poor pre-existing kidney function, acute respiratory distress syndrome).
- Patient shows signs of hypervolaemia (oedema in ≥2 dependent anatomical areas, radiological (ultrasound or X-ray) evidence of volume overload).

Fluid intake is minimised (eg, drug infusions). Compression stockings/bandages are applied in case of leg oedema (unless there are contraindications: peripheral arterial disease of any stage, history of peripheral bypass, local skin or soft tissue conditions such as open venous pressure ulcers, etc). All patients receive furosemide starting from 40 mg every 6 hours (or 10 mg/hour per infusion pump) up to 250 mg every 6 hours (or 60 mg/hour per infusion pump) (maximal daily dose is 1500 mg/24 hours) (=conservative treatment bundle, also see figure 1). The furosemide dose is titrated on effect (fluid output must exceed fluid input).

Mechanical fluid removal will be commenced in case the patient is already on RRT or has a life threatening FO (compartment syndrome, severe respiratory distress syndrome) with a significantly reduced renal function (ie, estimated glomerular filtration rate (eGFR) $<$15 mL/min), or has a refractory oliguria ($>$24 hours) non-responsive to conservative treatment.

Diuretics or mechanical fluid removal will be reduced or stopped in case a patient shows signs of impaired perfusion (see Part A).

Control group

All patients in the control group will be treated according to the standard of care. Currently, the standard of care is based on the ‘Surviving Sepsis Guidelines’. There is no upper limit for the use of intravenous or oral/enteral fluids in this group.

Safety measures

We defined safety measures for patients developing hypernatraemia, signs of impaired perfusion, hypokalaemia or severe metabolic alkalosis during the de-resuscitation phase.

Outcome measures

Primary outcome

The primary endpoint of this trial is the proportion (%) of patients with a negative cumulative fluid balance at day 3 after ICU admission.

Secondary outcome

- Number of patients with FO at day 3 and ICU discharge.
- Feasibility of the REDUCE fluid protocol (eg, number of REDUCE fluid protocol violations).
- Incidence of ischaemic events and severe acute kidney injury (AKI) during ICU stay: Number of patients with ischaemic events, severe AKI (Acute Kidney Injury Network (AKIN) stage 2 or more); respectively episodes of: severe hypernatraemia (sodium ≥155 mmol/L), severe hypokalaemia (<3.0 mmol/L), severe metabolic alkalosis (pH ≥7.55, bicarbonate ≥55 mmol/L), anaphylactic reaction to diuretic drug.
- Ventilator-free days up to day 30.
- Vasopressor-free up to day 30.
- RRT: Need for and time on RRT.
- Number of patients with need for renal replacement at day 90.
- All-cause mortality at day 30 and day 90.

Other outcome measures

Daily cumulative fluid balance up to day 7 of ICU stay.

Exploratory outcomes

Exploratory endpoints are the impact of the REDUCE protocol on inflammatory and endothelial markers.

Patient and public involvement

In the present study, no patient advisers or public was involved. The results of the REDUCE trial will be...
published in an international peer-reviewed medical journal regardless of the results.

Data collection
Data will be obtained from the participant’s hospital files, and national registries (mortality data) and entered in the web-based electronic case report form (eCRF) by trial investigators or their delegates. For participants transferred from our ICU to a non-trial ICU, data related to the outcomes will be collected by contacting the non-trial ICU. Data will be obtained on baseline parameters (e.g., age, sex, height, weight, severity of illness scores, comorbidities, medications, laboratory parameters, source of admission). In addition, daily data will be collected on fluid intake and losses, need for organ support (e.g., vasopressors, RRT), protocol violation and safety measures for up to day 30 or ICU discharge if prior to day 30. All data will be coded and entered in REDCap (V.12.4.12). All study data are archived for 10 years after study termination or premature termination of the study.

Blood sampling
From enrolment until the end of the de-resuscitation phase or day 7, patients will have daily blood samplings for creatinine, urea and uric acid. One urine sample in the resuscitation phase every 2 hours for 24 hours and 8 hourly thereafter until the end of the de-resuscitation phase or day 7. Additional blood samples will be drawn at the main study centre at four defined time points (baseline, days 2, 3 and 7).

Follow-up
Data on discharge from ICU and hospital, and in case of transfer to another hospital, date of ICU and hospital discharge from that hospital will be collected. In addition, death (yes or no) and requirement of ongoing RRT on day 90 after randomisation.

Monitoring
The trial will be externally monitored according to the good clinical practice (GCP) directive and the monitoring and data verification plan including the documentation of informed consent of trial participants.

Statistical analysis
Determination of sample size
We intend to enrol 170 patients to show an increase in the proportion of patients with a negative fluid balance on day 3 after ICU admission from 30% to 50% (power of 0.8), including a 15% dropout rate. The estimation is based on previous trials, as well as data from our ICU, which has shown that about one-third of patients with septic shock achieve a negative cumulative fluid balance on day 3.\(^\text{14, 41}\) We have chosen day 3, as previous studies have shown a better survival in patients with septic shock with achieving a negative cumulative fluid balance on day 3 after ICU admission.\(^\text{14, 42}\) The sample size calculation was performed by the CTU of the University of Bern and was computed using Stata, V.16.1, applying Pearson’s \(\chi^2\) test.

Planned analyses
All randomised patients receiving the study intervention will be included into the analysis in an intention-to-treat (ITT) analysis.\(^\text{43}\) Per-protocol (PP) analyses are performed in the population which excludes patients with protocol violations. Variables are presented with mean and SD or as medians with IQRs as appropriate.

Whether the REDUCE protocol significantly increased the proportion of patients with a cumulative negative fluid balance on day 3 after ICU admission (primary outcome) will be assessed by a logistic regression model adjusting for the stratification variables (trial site and chronic renal failure) in the ITT population.\(^\text{44}\) We will report absolute risk difference and relative risk ratios with 95% CI for the primary analysis of the primary outcome. Sensitivity analyses of the primary outcome will be performed using a logistic regression model adjusted for appropriate confounders. PP analyses are additionally adjusted for pre-randomisation variables which are predictive for non-protocol adherence.\(^\text{15}\)

Our secondary endpoints will be assessed by generalised regression models adjusting for stratification variables (ITT analysis) and additional pre-randomisation variables (PP analysis). We will use gamma regression models for ventilator-free days, vasopressor-free days and time on RRT, logistic regression models for the need of RRT and all-cause mortality and Gaussian regression models for fluid balance. We will report absolute risk difference and relative risk ratios with 95% CIs for dichotomous secondary outcomes. For continuous secondary outcomes we will report mean differences with 95% CIs.

P values will be two-tailed and p values smaller than 0.05 are considered statistically significant for the primary outcome, while secondary outcomes will be analysed in an explorative way.

Missing data and dropouts
In case of missing data (cut-off >5% missingness), a multiple imputation approach will be used. If the rate of dropouts before day 3 exceeds the estimated amount of 15%, new patients will be randomised to assure adequate power.

Interim analyses
We plan to conduct interim analysis after enrolment of 50% of the patients (n=85) to assess safety and feasibility outcomes.

DISCUSSION
Although intravenous fluid therapy is the most common treatment in critically ill patients, little is known about how to maximise benefits and minimise harms. The currently recommended fluid administration in patients with septic
shock frequently contributes to a positive fluid balance and thus development of FO.\textsuperscript{4, 8, 40} Recent studies show a consistent association between FO and poor outcomes including mortality in critically ill patients.\textsuperscript{9, 11, 13} especially in the subgroup of patients with septic shock.\textsuperscript{7, 8} Importantly, a recently published trial in patients with acute pancreatitis, a disease sharing many pathophysiological features with septic shock, had to be stopped as liberal fluid administration led to more harm without benefit compared with restrictive fluid administration.\textsuperscript{11}

Fluid restriction in the early phase of septic shock has been shown to be feasible and safe,\textsuperscript{12, 15, 16} however a survival benefit could not be shown. However, studies on de-resuscitation strategies in patients with septic shock are scarce and high-quality randomised controlled trials (RCTs) are lacking.\textsuperscript{17}

Silversides and colleagues have evaluated active fluid removal on the general ICU population and could show a significant fluid separation in the intervention group.\textsuperscript{20} The latter trial combined pharmacological with mechanical (RRT) measures to achieve de-resuscitation.\textsuperscript{20} In addition, a large multicentre study in the general ICU population investigating early goal-directed therapy with furosemide (GODIF trial) is currently carried out.\textsuperscript{47} In contrast to the two trials mentioned, our trial focuses on patients with septic shock, a specific pathophysiological entity, especially prone to FO.\textsuperscript{8, 11, 17} In addition, this trial follows a multitier, multimodal approach using a restrictive fluid management regime in the early phase of septic shock combined with a bundle of physical (compression stockings), pharmacological and mechanical measures and creep fluid minimisation.

The REDUCE RCT will provide high quality evidence whether a multitier, multimodal structured and early de-resuscitation strategy is feasible and safe in the critically ill with septic shock. If our protocol proves feasible, a multicentre randomised controlled clinical trial investigating whether the REDUCE fluid management protocol lowers mortality in critically ill patients with sepsis will be planned. In any case, the results of this study will be published in a peer-reviewed scientific journal.

**Perspective**

The REDUCE trial combines the two strategies to minimise FO ‘restrictive fluid administration and early fluid removal’ in a multitier, multimodal approach. Our REDUCE fluid protocol is pragmatic and thus usable in everyday clinical practice and will provide evidence on the effect of structured fluid administration in patients with septic shock.

**Ethics considerations**

The lead ethical committee of the Canton Bern approved the study and all participating centres (No 2020–02197). The trial is registered on ClinicalTrials.gov (date of registration 18 June 2021). Individual consent will be sought from all trial participants (see online supplemental material). In case the patient is unable to provide informed consent for the study at the time of ICU admission as a consequence of mental incapacity due to the underlying medical condition and treatment, consent from an independent physician will be obtained, in accordance with Swiss law, followed by (as soon as possible) proxies’ consent, and deferred subject consent, as soon as the patient’s conditions allows, in a later phase.

**Dissemination**

The results of the REDUCE trial will be published in an international peer-reviewed medical journal regardless of the results. The reporting of our results will be in adherence to the Consolidated Standards of Reporting Trials statement.\textsuperscript{48}

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8Competing interests

AM is the principal investigator and CAP is the sponsor for the trial. The trial protocol and the REDUCE fluid protocol were developed by AM and CAP. AM and CAP drafted the protocol paper. All co-investigators of the REDUCE trial (UP, MS, PB, JW, MM, DU, AH, MF, DB and JCS) have reviewed the manuscript for important intellectual content. CAP and AM revised in light of comments from all co-investigators. All authors approved the final version of the manuscript.

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**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

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**Supplemental material**

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