RESEARCH PROTOCOL

Practice of Fluid Therapy in Critically Ill Invasively Ventilated Patients (PRoFLUID)—an international multicenter observational cohort study

The PRoFLUID–investigators

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PROTOCOL TITLE: Practice of Fluid Therapy in Critically Ill Invasively Ventilated Patients (PRoFLUID)—an international multicenter observational cohort study

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ARDS	Acute Respiratory Distress Syndrome
CFB	Cumulative Fluid Balance
DSMB	Data Safety Managing Board
HIC	High–income Country
ICH–GCP	International Committee on Harmonization–Good Clinical Practice
ICU	Intensive Care Unit
IRB/IEC	Institutional Review Board/Institutional Ethical Committee
LMIC	Low– and Middle–income Country
MAP	Mean Arterial Pressure
PaO_2	Arterial partial pressure of oxygen
PRoFLUID	PRactice of FLUID therapy in critically ill invasively ventilated patients
RASS	Richmond Agitation Sedation Scale
SpO_2	Peripheral Arterial Oxygen Saturation
$S(c)VO_2$	(Central) Venous Oxygen Saturation
SOFA score	Sequential Organ Failure Assessment score

1. SUMMARY

Rationale

The worldwide practice of fluid and vasopressor therapy in critically ill invasively ventilated patients is uncertain. Indeed, it is unclear whether there is a difference in fluid and vasopressor therapy in these patients between Low– and Middle–income Countries (LMICs) and High–income Countries (HICs).

Objective

To determine various aspects of fluid and vasopressor therapy in critically ill invasively ventilated patients in LMICs and HICs.

Hypothesis

There is substantial worldwide variation in practice of fluid and vasopressor therapy in critically ill invasively ventilated patients.

Study design

International, multicenter, observational study in critically ill invasively ventilated patients; data are captured during a predefined period per geographic region or country.

Study population

Critically ill invasively ventilated patients.

Main study parameter/endpoint

The primary outcome is a composite of various aspects of fluid therapy, including total volumes of types of fluids administered in the first three days after start of invasive ventilation and total volume of fluids infused in the first seven days after start of invasive ventilation. Secondary outcomes include timing of start, type, and duration of continuous administration of vasopressors; timing of start, infusion time and types of administered diuretics; daily urine output and cumulative fluid balances; and typical ICU outcomes, like duration of ventilation, lengths of stay in ICU and hospital, and mortality in the ICU and hospital, and at day–28, –60 and –90.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Because of the observational design of the study using routinely collected data, there is no additional burden for the patient. Collection of data from ICU charts or electronic medical records systems is of no risk to the patients.

2. INTRODUCTION AND RATIONALE

2.1. Temporal changes in fluid therapy in critically ill invasively ventilated patients

Intravenous fluid is among the most prescribed medications in the intensive care unit (ICU). Most is used intentionally, to improve hemodynamics in patients with hypotension or hypoperfusion, and to compensate for lost fluids (1). A smaller amount is administered unintentionally, as a vehicle for medication or to maintain catheter patency (2). Intravenous fluid administration was once considered to be 'harmless'. However, in recent years it became clear that fluid therapy has important side–effects. The paradigm of 'liberal fluid administration' in critically ill patients has been challenged, and novel concepts such as 'restricted fluid administration', defined as minimizing fluid intake while maintaining organ perfusion (3), 'timely deresuscitation', defined as early and active removal of fluid after initial resuscitation (4), and 'fluid tolerance', defined as the degree to which a patient can tolerate fluid administration without causing organ dysfunction (5-7), were introduced.

As there are complex interactions between invasive ventilation and fluid status, fluid therapy in invasively ventilated patients is even more challenging. Invasive ventilation disrupts fluid homeostasis and predisposes to hemodynamic intolerance of hypovolemia (8). Conversely, hypervolemia can lead to pulmonary edema resulting in an impaired gas–exchange and worsened pulmonary compliance, jeopardizing lung–protective ventilation (8).

The type of fluid has also been subject of discussion. While initially thought to be beneficial, synthetic colloidal solutions not only have no benefit over crystalloid solutions (9-11), but even cause harm (12). Albumin solutions also have no benefit in unselected critically ill patients, and may only improve outcome in patients with septic shock but are considered harmful in patients with traumatic brain injury (13, 14). Crystalloid solutions are now first choice (15). While balanced crystalloid solutions were initially thought to prevent kidney injury (16), they do not clearly improve outcomes and may even be harmful for traumatic brain injury patients (17, 18).

2.2. Liberal *vs* restrictive fluid strategy

Optimizing tissue perfusion while preventing fluid overload can be highly challenging in critically ill invasively ventilated patients. A liberal fluid strategy often results in a positive cumulative fluid balance (CFB). A positive CFB is associated with worse outcomes in the ICU. For instance, CFB is associated with mortality and duration of

ventilation in invasively ventilated patients with the acute respiratory distress syndrome (ARDS) (19, 20). In critically ill patients with sepsis, a positive CFB is associated with mortality and kidney dysfunction (21-24). One meta–analysis of randomized clinical trials in critically ill sepsis patients in fact showed benefit of a restrictive fluid strategy combined with early deresuscitation following the resuscitation phase with respect to duration of ventilation and ICU length of stay (25).

2.3. Early *vs* late start of vasopressor therapy

Vasopressors are often used in conjunction with intravenous fluids to treat hypotension. Previously, vasopressor therapy was started only after 'sufficient' fluid administration and through a central venous route. Recent studies, however, suggest that an earlier start of vasopressor therapy leads to faster correction of hypotension, and prevents infusion of large volume of intravenous fluids (26-28). The 'Surviving Sepsis Campaign' guideline now recommends starting vasopressor therapy as soon as possible in hypotensive patients, even if it means administering it through a peripheral venous route (29). Herein, norepinephrine is the first choice vasopressor in most critically ill patients, due to a better safety profile compared to dopamine or epinephrine (30). Vasopressin can be added to norepinephrine when hypotension is refractory to initial therapy (31).

2.4. Geographic and geo–economic differences in fluid and vasopressor therapy

A large geographical variation in fluid therapy has been described. One study in 2014 showed that critically ill patients were most often prescribed albumin solutions in Australia, normal saline solutions in France and balanced solutions in Germany (32). In resource–limited ICUs certain types of fluids and vasopressors are given less often than in resource–rich ICUs due to differences in the supply chains, shortages and costs (33). While some colloidal solutions are no longer available for use in critically ill patients in the European Union, these harmful fluids might now be marketed in low– and middle–income countries (LMICs) (34). Last but not least, peripheral administration of vasopressors might be more common in LMICs due to the restricted use of central venous catheters.

2.5. Why this service review of fluid and vasopressor therapy?

Currently, we are uncertain how fluid and vasopressor therapy is practiced worldwide. Many aspects of fluid and vasopressor therapy have been challenged in recent years and critical care physicians remain highly divided on which approach is best (35), within and between countries (36). Furthermore, actual practice might be substantially

different from what is expected from the literature (36). The here proposed worldwide observational study in critically ill invasively ventilated patients on fluid and vasopressor therapy will provide a better insight in current and local practices, may show certain aspects of fluid and vasopressor therapy to have associations with clinical outcomes, and helps in the planning of future clinical trials in this field.

3. AIMS AND HYPOTHESES

3.1. Aims

To determine the current practice of fluid and vasopressor therapy in critically ill invasively ventilated patients (primary); to compare fluid and vasopressor therapy between Low– and Middle–income Countries (LMICs) and High–income Countries (HICs) and to determine the associations of various aspects of fluid and vasopressor therapy with clinical outcomes.

3.2. Hypotheses

There is large variation in fluid and vasopressor therapy in critically ill invasively ventilated patients (primary); there are differences in fluid and vasopressor therapy between LMICs and HICs; certain aspects of fluid and vasopressor therapy have an independent association with clinical outcomes.

4. STUDY DESIGN

Prospective, international, multicenter, observational study in critically ill invasively ventilated patients during a 28–day period in a convenience sample of hospitals globally.

5. STUDY POPULATION

5.1. Population (base)

We will collect data in critically ill invasively ventilated patients that receive ventilation for at least 24 hours. We expect a minimum of 200 ICUs from 30 countries to participate in this prospective international multicenter observational study. Patients will be screened daily during a 28–day period. A registry of limited demographic data will be compiled on all screened patients. Data regarding fluid administration, vasopressor use, diuretics use, oxygen exchange, and kidney function will be collected daily from the start of invasive ventilation. Collection will be retrospective, for the previous day. Clinical complications will be evaluated on day 90 day after start of invasive ventilation, death or hospital discharge, whichever comes first.

5.2. Inclusion criteria

- admitted to a participating ICU;
- receiving invasive ventilation within 3 days of ICU admission; and
- duration of ventilation > 24 hours;

5.3. Exclusion criteria

- age < 16 years;
- patients transferred under invasive ventilation from another ICU;

5.4. Randomization

Not applicable

5.5. Sample size calculation

No formal sample size calculation is necessary for the primary endpoint. However, for investigating associations of aspects of fluid and vasopressor therapy with mortality using logistic regression and adjusting for a limited set of pre-specified confounders, we estimate to need 150 ‘events’ using the 10 event per variable rule of thumb. As fluid and vasopressor management is particularly important in patients with acute respiratory distress (ARDS), we will need at least 150 events in this subgroup. With an incidence of ARDS of approximately 20% and a mortality rate of 30%, we estimate to need 2500 patients to have 150 events in patients with ARDS (37). Assuming that a participating ICU has 50 unique admissions in 4 weeks on average, of which 25% is invasively ventilated for > 24 hours, we expect to need a minimum of 200 participating ICUs (38-40).

6. METHODS

6.1. Study parameters

6.1.1. Primary parameter

- Quantity, timing and type of intravenous fluids administered.

6.1.2. Secondary study parameters

- Time of start of vasopressors;
- Route of administration for vasopressors (i.e. central vs. peripheral route);
- Types of vasopressor used;
- Daily urine output;
- Cumulative fluid balance;
- Timing of start, type and infusion time (i.e. bolus vs. continuous infusion) of administered diuretic;
- Incidence of atrial arrhythmias;
- Incidence of acute respiratory distress syndrome (ARDS)
- Incidence of renal replacement therapy;
- Incidence of persistent renal dysfunction, defined as the need for renal replacement therapy at ICU discharge;
- ICU length of stay, defined as the time between ICU admission and discharge or death;
- Hospital length of stay, defined as the time between hospital admission and discharge or death;
- Duration of ventilation, defined as the time between initiation of invasive ventilation and successful liberation of ventilation.
- Ventilator–free days and alive at day 28, defined as 28 - x if successfully liberated from ventilation x days after initiation. If subject dies within 28 days ventilator–free days is set to 0;
- All–cause ICU mortality, defined as any death during ICU stay;
- All–cause in–hospital mortality at day 28, defined as any death during hospital stay before or on study day 28;
- All–cause in–hospital mortality at day 60, defined as any death during hospital stay before or on study day 60;
- All–cause in–hospital mortality at day 90, defined as any death during hospital stay before or on study day 90;

6.2. Study procedures

Patients in participating centers are screened on a daily basis. Eligible patients are included during the 28–day observation period, from Monday at 8:00 AM to the Monday four weeks later at 7:59 AM (in time zones of the participating centers). The timing of the 28–day observation period will be flexible for participating centers and determined at a later stage together with the international study–coordinator and each national investigator. Times points of data collection:

- Demographic and baseline data are collected from the clinical files – at ICU admission;
- Types, quantities, of administered fluids– during the first three calendar days with high-granularity. From day 4-7 lower granularity data concerning the total volume of infused fluids will be collected;
- Types and modalities of administration of vasopressors – over a maximum of seven days of ICU admission;
- Vital signs, laboratory results and limited treatment parameters are collected – once daily for a maximum of seven days;
- Cumulative fluid balance – calculated once a day on a time point convenient per each center for a maximum of seven days; and
- Outcomes – recorded at 90 days, the day of death or hospital discharge, whichever comes first.

6.2.1. Inclusion

During a 28–day period, all admitted patients are screened daily by a local investigator. To reduce workload in high-volume ICU's, local investigators can opt to stop study screening and enrollment after every 20 participants. However, once committed to a 20-participant block, researchers must continue until its completion before reassessing.

6.2.2. Collection of data

Data is collected from the patient medical chart, unless a local electronic system to register data can be used (e.g., patient data management system). Local investigators transcribe the collected data onto an Internet–based electronic CRF (Castor Electronic Data Capture). Access to the data–entry system is protected by a personalized username and password.

6.2.3. Data to be collected

The following data will be collected for all enrolled patients admitted to ICU during the screening period. Day 0 is defined as the day of initiation of invasive ventilation. Day 1 is defined as the first full calendar day after initiation of invasive ventilation. In patients that are not invasively ventilated at ICU admission day -3 to -1 are defined as the days before intubation but after ICU admission.

A. At ICU admission;

- Gender, male/female/other;
- Age, years;
- Weight, kg;
- Length, cm;
- Ethnicity, Black, East Asian, Indigenous (First Nations, Inuk/Inuit, Métis), Latin American, Middle Eastern, South Asian, Southeast Asian, White;
- Reason for ICU admission;
- Traumatic brain injury?;
- Sub-arachnoid hemorrhage?
- Date of ICU admission;
- Date of start of invasive ventilation;
- Did the patient receive non-invasive ventilation or high-flow nasal oxygen prior to intubation, if so: on which day?;
- Serum creatinine, µmol/L or mg/dL, lowest in the last year, if available; and
- If the reason for ICU admission was burns: what was the cause of the burn and how much total body surface area is affected by the burns
- If the reason for ICU admission was sepsis, what was the focus of the sepsis (e.g. respiratory, abdominal)

B. On day 0;

- Type and volume, ml, of each fluid infusion (including medication and parenteral nutrition);
- Type and volume of oral fluids;
- Anuria ≥ 12 hours?, yes/no;
- Urine output, ml, over 24 hours;
- Extracorporeal life support, venoarterial/venovenous/no;

- Renal replacement therapy, yes/no, if yes;
  - Volume extracted by ultrafiltration, ml, over 24 hours;
- Cumulative fluid balance, ml;
- Loop diuretics given, yes/no, if yes;
  - Furosemide, yes/no, if yes;
  - (if no furosemide used) Bumetanide, yes/no, if yes;
  - (if no bumetanide or furosemide used) Torasemide, yes/no, if yes;
  - (if no Torasemide, bumetanide, furosemide used) Edecrin, yes/no;
- Additional diuretic given (thiazide, carbonic anhydrase inhibitor or mineralocorticoid antagonist), yes/no;
- Serum creatinine, µmol/L or mg/dL, at a convenient fixed time point;
- Serum hemoglobin, µmol/L or mg/dL, at a convenient fixed time point;
- Serum albumin, at a convenient fixed time point;
- Vasopressors initiated, yes/no, if yes;
  - Time between ICU admission and initiation of vasopressors, hours;
  - Drug(s) used as vasopressor;
- Mean arterial pressure (MAP) mmHg, at a convenient fixed time point;
- Heart rate, beats/min, at a convenient fixed time point;
- Atrial fibrillation or flutter during the last day, yes/no;
- Arterial or venous lactate, if measured, mmol/L, highest and lowest value;
- (Central) venous oxygen saturation (S(c)VO_2), mmol/L, if measured, highest and lowest value;
- Arterial partial pressure of oxygen (PaO_2), kPa or mmHg, at a convenient fixed time point;
  - (if no PaO_2 is known) Peripheral arterial oxygen saturation (SpO_2), percentage, at a convenient fixed time point;
- Inspired oxygen fraction, %, at time of PaO_2 or (if no PaO_2 is known) SpO_2;
- Suspected or confirmed infection that causes organ dysfunction (sepsis) yes/no;
- Was there new-onset (<7 days) respiratory symptoms, or acute worsening of respiratory symptoms?, yes/no, if yes;
- Are there bilateral opacities on chest imaging (including lung ultrasound),yes/no;
- If there was hypoxemia, was the hypoxemia explained by cardiac failure, yes/no?

- Richmond Agitation Sedation Scale (RASS), highest value of this day after intubation; and
- Sequential Organ Failure Assessment (SOFA) score.

C. Daily on day 1 and day 2;

- Type, volume, ml, and rate, ml/min, of each separate fluid infusion (including medication and parenteral nutrition);
- Type and volume of oral fluids;
- Anuria ≥ 12 hours?, yes/no;
- Urine output, ml, over 24 hours;
- Extracorporeal life support, venoarterial/venovenous/no;
- Renal replacement therapy, yes/no, if yes;
    - Volume extracted by ultrafiltration, ml, over 24 hours;
- Cumulative fluid balance, ml;
- Loop diuretics given, yes/no, if yes;
    - Furosemide, yes/no, if no;
        - (if no furosemide used) Bumetanide, yes/no, if no;
        - (if no bumetanide or furosemide used) Torasemide, yes/no;
        - (if no Torasemide, bumetanide, furosemide used) Edecrin, yes/no;
    - Additional diuretic given (thiazide, carbonic anhydrase inhibitor or mineralocorticoid antagonist), yes/no;
- Serum creatinine, µmol/L or mg/dL, at a convenient fixed time point;
- Serum hemoglobin, µmol/L or mg/dL, at a convenient fixed time point;
- Serum albumin, at a convenient fixed time point;
- Vasopressors given, yes/no, if yes;
    - Time between ICU admission and initiation of vasopressors, only if not initiated on day 0, hours;
    - Drug(s) used as vasopressor;
- MAP, mmHg, at a convenient fixed time point;
- Heart rate, beats/min, at a convenient fixed time point;
- Atrial fibrillation or flutter during the last day, yes/no;
- Arterial or venous lactate, mmol/L, at a convenient fixed time point;
- Serum sodium, mmol/l, at a convenient fixed time point;

- Serum chloride, mmol/l, at a convenient fixed time point;
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- S(c)VO_2, mmol/L, highest and lowest value;
- PaO_2, kPa or mmHg, at a convenient fixed time point;
  - (if no PaO_2 is known)) Peripheral arterial oxygen saturation (SpO_2), percentage, at a convenient fixed time point;
- Inspired oxygen fraction, %, at time of PaO_2 or (if no PaO_2 is known) SpO_2;
- Was there new-onset (<7 days) respiratory symptoms, or acute worsening of respiratory symptoms?, yes/no, if yes;
- Are there bilateral opacities on chest imaging (including lung ultrasound), yes/no;
- If there was hypoxemia, was the hypoxemia explained by cardiac failure, yes/no?
- Richmond Agitation Sedation Scale (RASS), highest value of the day; and
- SOFA score.

D. Daily on day 3 to 7 or ICU discharge; and on day -1, day -2 and day -3;

- Total volume of infused fluid, ml, over 24 hours
- Cumulative fluid balance, ml, over 24 hours;
- Urine output, ml, over 24 hours;
- Extracorporeal life support, venoarterial/venovenous/no;
- Renal replacement therapy, yes/no, if yes;
  - Volume extracted by ultrafiltration, ml, over 24 hours;
- Loop diuretics given, yes/no, if yes;
  - Furosemide, yes/no, if no;
  - (if no furosemide used) Bumetanide, yes/no, if no;
  - (if no bumetanide or furosemide used) Torasemide, yes/no;
  - (if no Torasemide, bumetanide, furosemide used) Edecrin, yes/no;
  - Additional diuretic given (thiazide, carbonic anhydrase inhibitor or mineralocorticoid antagonist), yes/no;
- Serum creatinine, µmol/L or mg/dL, at a convenient fixed time point;
- Serum hemoglobin, µmol/L or mg/dL, at a convenient fixed time point;
- Serum albumin, at a convenient fixed time point;
- Vasopressors used, yes/no, if yes;
  - Drug(s) used as vasopressor;

- MAP, mmHg, at a convenient fixed time point;
- Heart rate, beats/min, at a convenient fixed time point
- Atrial fibrillation or flutter during the last day, yes/no;
- Arterial or venous lactate, mmol/L, at a convenient fixed time point;
- Serum sodium, mmol/l, at a convenient fixed time point;
- Serum chloride, mmol/l, at a convenient fixed time point;
- PaO_2, kPa or mmHg, at a convenient fixed time point;
  - (if no PaO_2 is known)) Peripheral arterial oxygen saturation (SpO_2), percentage, at a convenient fixed time point;
- Inspired oxygen fraction, %, at time of PaO_2 or (if no PaO_2 is known) SpO_2; and
- SOFA score.

E. Events (at day 7 or ICU discharge, whichever comes first)

- Were vasopressors initiated before ICU admission?, yes/no;
  - If no: Date of initiation of vasopressors after ICU admission, date;
- Route of initiation of vasopressors, central venous/peripheral venous;
- Did the patient develop AKI; yes/no;
  - if yes, on which study day?, day;
- Did the patient develop rhabdomyolysis; yes/no;
  - if yes, on which study day?, day;
- If the patient was admitted for sepsis, what was the suspected or proven pathogen causing the sepsis?

F. Follow-up (at hospital discharge, day 90, or death, whichever comes first)

- Vital status, alive/dead, if dead;
  - Date of death;
- Reintubation, yes/no, if yes;
  - Number of reintubations;
  - Date of initial extubation;
  - Date of reintubation;
- Date of last extubation (or in the case of tracheostomy 24 hours without support from the ventilator);
- Date of ICU discharge;

- Date of hospital discharge; and
- Subjects requires renal replacement therapy or hemodialysis, yes/no.

6.2.4. Follow–up

Participants are subject to follow–up until hospital discharge, day 90 or death.

7. SAFETY REPORTING

7.1. Adverse and serious adverse events

Not applicable

7.2. Follow–up of adverse events

Not applicable

7.3. Data Safety Management Board (DSMB)

Not applicable

8. STATISTICAL ANALYSIS

8.1. Descriptive statistics

Data are expressed as means (standard deviation), medians (interquartile range) and proportions as appropriate. Mann–Whitney U–tests are used to compare continuous variables and Fisher's exact tests are used for categorical variables. Comparisons between and within groups are performed using one–way ANOVA with post–hoc analyses for continuous variables.

8.2. Plan of analysis

Subjects that are transferred to another ICU in the first three calendar days of ICU admission will be excluded from analysis. Subjects that are transferred to another ICU after the first three calendar days, but before seven days are excluded from analysis of the secondary endpoints. Patients admitted due to pancreatitis, burns, diabetic ketoacidosis, severe rhabdomyolysis and sub-arachnoid bleeding will be analyzed separately and excluded from analysis if less than 30 subjects are included in each category. Subjects diagnosed with sepsis or ARDS during the first three calendar days of ICU admission will be part of a subgroup analysis. Associations with outcomes will be assessed through regression modelling. Time to event variables are analyzed using Cox regression and visualized by Kaplan–Meier plots. For each analysis proposed, a complete statistical analysis plan will be prepared, finalized and made available before starting the analyses. Statistical analyses are conducted using R (www.r-project.org). A *P*–value of less than 0.05 is considered statistically significant.

9. ETHICAL CONSIDERATIONS

9.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil 2013. Data management, monitoring and reporting of the study will be performed in accordance with the International Conference on Harmonization – Good Clinical Practice (ICH–GCP) guidelines.

This project does not subject participants to an intervention. Also, this study does not require additional blood collection, or other diagnostic procedures.

9.2. Ethical and Regulatory authorities' approval

The study protocol is submitted to the IRB of the Amsterdam UMC for ethical review. All participating centers must submit the study protocol to the local Institutional Review Board for ethical judgment and obtain document of proof that the trial has been subject to Institutional Review Board/Institutional Ethical Committee (IRB/IEC) review. Considering that all study data is recorded from medical charts and no additional data collection or patient assessment is performed, ethical approval may not be required in some centers. However, where ethical approval is required, this approval must be obtained before the start of inclusion.

If authorization/approval/notification by the regulatory authorit(y)(ies) is applicable locally, this document should be obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s).

9.3. Patient information and informed consent

Only if applicable, informed consent forms and any other written information to be provided to the subjects as well as advertisement for subject recruitment (if used) should be subject to IRB/IEC review and given approval/favorable opinion. If informed consent is not required by the local IRB, a waiver must be obtained from the Institutional Review Board.

The study coordinator provides a template of Patient Information Sheet and Participant's Informed Consent and Authorized Informed Consent in English

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1. Handling and storage of data and documents

All patients will be identified with a study identification code. The codebook will be stored digitally and in paper. The paper version will be stored behind a lock and the digital form will be encrypted with a double password. All de-identified data will be stored for the length of the study and for 20 years afterwards, for further publication. The codebook will be kept for 5 years after the end of the inclusion period. The study will be registered at ClinicalTrials.gov.

10.2. Public disclosure and publication policy

The results of this service review will be published in a peer–reviewed medical journal. All participants in the project will get credit for the publication. National coordinators and all local investigators will be granted collaborative authorship. After publication of the primary results, on request the pooled dataset will be available for all members of the PRoFLUID collaboration for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee. Before submission the final version of all manuscripts related to the PRoFLUID dataset must be approved by the Executive Steering Committee.

10.3. Organization

The role of the ***International coordinator*** is to centrally manage common scientific and administrative aspects related to the project. He will assist National coordinators in all phases of project start–up, ethical approvals submissions, patient inclusion and data monitoring. He will have direct administrator access to the web–based data management software and assist national and local coordinators in ensuring data safety and quality.

National coordinators will be appointed in each participating country. They will identify and recruit local participating centers. They will assist and train the site coordinators and oversee the conduct of the study according to ICH–GCP guidelines. They will ensure that all local necessary ethical and regulatory approvals are obtained before start of patient inclusion. They will assist and validate translation of study documents (protocol, CRF, patient informed consent form) and help coordinating data cleaning in their countries if needed.

Local investigators in individual participating centers will provide scientific and structural leadership in their center. They will ensure all local necessary ethical and regulatory approvals are obtained before start of patient inclusion. They will train and

monitor their local research group, to ensure the study is conducted according to ICH–GCP guidelines. They guarantee the integrity of data collection and ensure timely completion of CRFs.

11. REFERENCES

1. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care. 2010;14(5):R185.
2. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. Intensive Care Med. 2018;44(4):409-17.
3. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564-75.
4. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014;46(5):361-80.
5. Malbrain MLNG, Martin G, Ostermann M. Everything you need to know about deresuscitation. Intensive Care Medicine. 2022;48(12):1781-6.
6. Kattan E, Castro R, Miralles-Aguiar F, Hernández G, Rola P. The emerging concept of fluid tolerance: A position paper. Journal of Critical Care. 2022;71:154070.
7. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nature Reviews Nephrology. 2018;14(9):541-57.
8. Tobin MJ. Principles And Practice of Mechanical Ventilation, Third Edition: McGraw-Hill Education; 2013.
9. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care. 2012;16(3):R94.
10. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care. New England Journal of Medicine. 2012;367(20):1901-11.
11. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. New England Journal of Medicine. 2012;367(2):124-34.
12. Lewis SR, Pritchard MW, Evans DJW, Butler AR, Alderson P, Smith AF, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database of Systematic Reviews. 2018(8).
13. Investigators TSS. A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. New England Journal of Medicine. 2004;350(22):2247-56.
14. Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M, et al. Albumin Replacement in Patients with Severe Sepsis or Septic Shock. New England Journal of Medicine. 2014;370(15):1412-21.
15. Martin C, Cortegiani A, Gregoretti C, Martin-Loeches I, Ichai C, Leone M, et al. Choice of fluids in critically ill patients. BMC Anesthesiology. 2018;18(1):200.
16. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, et al. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018;378(9):829-39.
17. Zampieri FG, Machado FR, Biondi RS, Freitas FGR, Veiga VC, Figueiredo RC, et al. Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial. JAMA. 2021;326(9):818-29.

18. Finfer S, Micallef S, Hammond N, Navarra L, Bellomo R, Billot L, et al. Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults. New England Journal of Medicine. 2022;386(9):815-26.
19. Ahuja S, de Grooth HJ, Paulus F, van der Ven FL, Serpa Neto A, Schultz MJ, et al. Association between early cumulative fluid balance and successful liberation from invasive ventilation in COVID-19 ARDS patients - insights from the PRoVENT-COVID study: a national, multicenter, observational cohort analysis. Crit Care. 2022;26(1):157.
20. van Mourik N, Metske HA, Hofstra JJ, Binnekade JM, Geerts BF, Schultz MJ, et al. Cumulative fluid balance predicts mortality and increases time on mechanical ventilation in ARDS patients: An observational cohort study. PLoS One. 2019;14(10):e0224563.
21. Zhang L, Xu F, Li S, Zheng X, Zheng S, Liu H, et al. Influence of fluid balance on the prognosis of patients with sepsis. BMC Anesthesiology. 2021;21(1):269.
22. Acheampong A, Vincent J-L. A positive fluid balance is an independent prognostic factor in patients with sepsis. Critical Care. 2015;19(1):251.
23. van Mourik N, Geerts BF, Binnekade JM, Veelo DP, Bos LDJ, Wiersinga WJ, et al. A Higher Fluid Balance in the Days After Septic Shock Reversal Is Associated With Increased Mortality: An Observational Cohort Study. Crit Care Explor. 2020;2(10):e0219.
24. Mele A, Cerminara E, Häbel H, Rodriguez-Galvez B, Oldner A, Nelson D, et al. Fluid accumulation and major adverse kidney events in sepsis: a multicenter observational study. Annals of Intensive Care. 2022;12(1):62.
25. Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive Care Med. 2017;43(2):155-70.
26. Elbouhy MA, Soliman M, Gaber A, Taema KM, Abdel-Aziz A. Early Use of Norepinephrine Improves Survival in Septic Shock: Earlier than Early. Arch Med Res. 2019;50(6):325-32.
27. Bai X, Yu W, Ji W, Lin Z, Tan S, Duan K, et al. Early versus delayed administration of norepinephrine in patients with septic shock. Crit Care. 2014;18(5):532.
28. The National Heart L, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension. New England Journal of Medicine. 2023;388(6):499-510.
29. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Critical Care Medicine. 2021;49(11):e1063-e143.
30. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of Dopamine and Norepinephrine in the Treatment of Shock. New England Journal of Medicine. 2010;362(9):779-89.
31. Oba Y, Lone NA. Mortality benefit of vasopressor and inotropic agents in septic shock: a Bayesian network meta-analysis of randomized controlled trials. J Crit Care. 2014;29(5):706-10.
32. Hammond NE, Taylor C, Finfer S, Machado FR, An Y, Billot L, et al. Patterns of intravenous fluid resuscitation use in adult intensive care patients between 2007 and 2014: An international cross-sectional study. PLoS One. 2017;12(5):e0176292.
33. Schultz MJ, Dünser MW, Dondorp AM, Adhikari NKJ, Iyer S, Kwizera A, et al. Current Challenges in the Management of Sepsis in ICUs in Resource-Poor Settings

and Suggestions for the Future. In: Dondorp AM, Dünser MW, Schultz MJ, editors. Sepsis Management in Resource-limited Settings. Cham: Springer International Publishing; 2019. p. 1-24.
34. Roberts I, Shakur H, Bellomo R, Bion J, Finfer S, Hunt B, et al. Hydroxyethyl starch solutions and patient harm. The Lancet. 2018;391(10122):736.
35. Silversides JA, McAuley DF, Blackwood B, Fan E, Ferguson AJ, Marshall JC. Fluid management and deresuscitation practices: A survey of critical care physicians. J Intensive Care Soc. 2020;21(2):111-8.
36. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, et al. Fluid challenges in intensive care: the FENICE study: A global inception cohort study. Intensive Care Med. 2015;41(9):1529-37.
37. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315(8):788-800.
38. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016;315(8):788-800.
39. Madotto F, Pham T, Bellani G, Bos LD, Simonis FD, Fan E, et al. Resolved versus confirmed ARDS after 24 h: insights from the LUNG SAFE study. Intensive Care Med. 2018;44(5):564-77.
40. Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, et al. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study. The Lancet Respiratory Medicine. 2023.