SEPTIC STUDY

Protocol Number 22SM8039

Fluid Trial Manual

Effective Date: 10 November 2023

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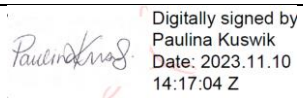
Paulina Kuswik	**Clinical Trial Monitor**		**10.11.2023**
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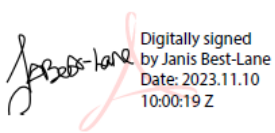
Janis Best-Lane	**Clinical Trial Manager**		**10.11.2023**

Contents

Associated Forms / Templates

1. Introduction

The purpose of this document is to describe the procedures involved in the Fluid Trial of the SepTiC Study.

2. Scope

The procedures outlined in this Fluid Trial Manual are applicable to all sites participating in the SepTiC study. This manual should be used alongside the SepTiC Protocol and eCRF Manual.

3. Abbreviations

ICTU	Imperial Clinical Trials Unit
SSPM	Study Specific Procedure Manual
SSC	Surviving Sepsis Campaign

4. Responsibilities

Investigator sites	• Ensure this Fluid Manual in combination with the protocol is followed when a patient is randomised to the intervention • To ensure any issues/confusion is highlighted to the trial team for clarification
Trial Manager/Monitor	• Monitor protocol adherence during on-site, remote and central monitoring techniques. • Ensure any updated documentation (such as this manual) or FAQs containing further clarification are shared with sites.

5. References

- Procedures for this manual have been taken from the SepTiC Protocol No: 22SM8039

6. Procedures

6.1. Randomisation

6.1.1. Eligibility

The patient must be eligible for the fluid trial prior to randomisation. The eligibility criteria are as follows:

Inclusion Criteria

- Adults (≥16 years of age) admitted to ICU due to suspected sepsis and expected to stay for at least two calendar days (i.e., expected to still to be in ICU the day after tomorrow).
- Receiving intravenous antibiotics for suspected sepsis
- According to local clinical judgement, patient has received adequate initial early fluid resuscitation (see below for further guidance and example on this point of the inclusion criteria)

Adequacy of fluid resuscitation is often subjective and difficult to judge, but the intention is that the initial very early rapid correction of hypovolaemia, sometimes referred to as the 'rescue' phase of fluid resuscitation, is complete. This is typically done within the first 3 hours from presentation. A volume of up to 30mL/kg would be typical of this 'rescue' phase, as described in SSC guidelines, but it is not essential that a specific volume of fluid has been given. The later 'optimisation' phase, where additional fluid boluses are more carefully titrated, is covered by the protocol, and randomisation should not be delayed just because the treating clinician believes that more fluid may be appropriate.

Example: an 80kg patient presents to ED with presumed sepsis and hypotension (85/45) associated with community-acquired pneumonia. After 2.5 litres of IV crystalloid given rapidly, blood pressure remains borderline (100/50) with evidence of shock (cold, mottled peripheries, elevated lactate, prolonged capillary refill time) and a further 250mL fluid bolus is prescribed while a noradrenaline infusion is set up.

Commentary: in this case the initial 'rescue' phase has been completed, and the clinical team are now uncertain about the effectiveness of further fluid boluses. The patient is suitable for enrolment to SepTIC on this criterion.

Exclusion Criteria

- More than 24 hours since ICU admission (this does NOT apply for GM-CSF).
- Previously admitted to ICU due to sepsis on this hospital admission
- Not expected to survive 90 days, due to pre-existing chronic (end-stage) disease
- Not expected to survive initial resuscitation (24 hours)
- Neutropaenia (<0.5 neutrophils x109 /L) due to chemotherapy/malignancy (but not due to sepsis)
- A source of infection that will require a prolonged course of antibiotics, for greater than 21 days (e.g., infective endocarditis, osteomyelitis, hepatic or cerebral abscess, tuberculosis)
- Diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar state (HHS)
- Within 21 days of a spontaneous subarachnoid haemorrhage
- Diabetes Insipidus
- Weight <40Kg

6.1.2. Randomisation on Open Clinica

- Instructions on randomisation can be found in the “eCRF completion guidelines”.
- Remember to complete the *Eligibility*, *Pre-Randomisation,* and *Fluid Randomisation Confirmation* for randomisation. Both Diagnostic and Fluid Randomisation **MUST** be completed at the same time.
- The randomisation result can be found in the “*Randomisation Assignment fluid*” form under allocation. The patient will be allocated to either “*Conservative fluid therapy with de-resuscitation”* or *“Standard Care”.*

6.2. Intervention – Conservative fluid therapy with de-resuscitation

6.2.1. Conservative fluid therapy (Day 1 – Day 5)

A conservative fluid strategy will be followed as soon as possible as after randomisation.

No routine maintenance fluids should be given.

Once initial early hypovolaemia has been corrected and in the absence of suspected or overt bleeding or other fluid loss, a 250ml bolus of an isotonic crystalloid may be given if any of the following objective signs of possible hypovolaemia are present:

- Skin mottling beyond the area of the kneecap
- Blood pressure target cannot be maintained despite up-titration or noradrenaline or other vasoactive drugs.
- Serum lactate ≥ 3 mmol/L
- Urine output < 0.25 ml/kg/h (on Day 1 only)

After administration of any fluid bolus, the patient should be re-assessed - have the original signs of hypovolaemia listed above been resolved?

Further fluid boluses may be given if, on re-assessment, signs of possible hypovolaemia remain. No maximum volume of fluid boluses is specified. However, if there is no improvement after such fluid boluses, (for example after four boluses, 1000mL), the likelihood of benefit from further fluid boluses is very low and should not be given.

No routine (maintenance) intravenous fluid will be given other than to correct electrolyte abnormalities or to prevent ketosis, although replacement of bleeding or measured external fluid losses (e.g., vomiting, nasogastric losses, drain fluid) of more than 0.5 litre/day may be given in a 1:1 ratio. Normal feeding will continue as per local ICU protocol.

If a patient is not absorbing enteral feeds and requires IV glucose, the suggestion would be to use 20% glucose (central line) or 10% (peripheral line) rather than 5% to halve / quarter the volume.

Intravenous drugs will be given in the smallest acceptable volumes.

6.2.2. Deresuscitation (Day 2-5)

On a daily basis (days 2-5), patients will be assessed for (1) fluid overload and (2) cardiovascular stability.

6.2.2.1 Fluid overload is defined as ANY ONE OF cumulative fluid balance > 3000mL, pulmonary oedema, or peripheral oedema in 2 or more sites (arms, legs, flanks, abdominal wall).

6.2.2.2 Cardiovascular stability is defined as norepinephrine requirement <0.2 mcg/kg/min and not increasing, AND no signs of hypovolaemia (skin mottling beyond the area of the kneecap, blood pressure target unable to be maintained despite up-titration or noradrenaline or other vasoactive drugs, serum lactate ≥ 3 mmol/L, or urine output < 0.25 ml/kg/h (on Day 1 only)

If fluid overload and cardiovascular stability are present, then de-resuscitation will be given.

If fluid overload is not present, or there is cardiovascular instability, diuretics should not be given, conservative fluid therapy should continue, and the patient should be reassessed the following day.

Deresuscitation will consist of combination diuretic therapy. The aim is for at least a negative fluid balance of 1000 ml/day. Combination diuretic therapy consists of:

- Oral indapamide* 5mg daily
- Furosemide 0.25mg/kg IV bolus (to the nearest 10mg, maximum 40mg)
- Furosemide infusion starting at 5mg/hr, titrated between 2-20mg/hr.

* Or any equivalent thiazide diuretic e.g., metolazone 5mg OD / bendroflumethiazide 5mg OD.

Note, if there is excessive diuresis resulting in a larger negative balance or the patient develops cardiovascular instability the furosemide infusion should be reduced or stopped.

The conservative fluid therapy with de-resuscitation will continue until day 5 or the patient is discharged from ICU, whichever comes first. Thereafter, fluids and diuretics will be given at the discretion of the clinical team, although we strongly recommend that care is taken to avoid (re) occurrence of fluid overload.

6.2.3. Renal replacement therapy

Patients requiring renal replacement therapy will not receive diuretics, but the clinicians will use a similar strategy. There will be daily re-assessment on days 2-5 according to previous criteria (fluid overload and cardiovascular stability), and if both fluid overload and cardiovascular stability are present, a similar negative balance (at least 1000mL/day) should be targeted through ultrafiltration (fluid removal).

If fluid overload (as defined above) is not present, or the patient has cardiovascular instability, conservative fluid therapy should be continued, and daily reassessment should continue.

6.2.4. Troubleshooting / Common complications

6.2.4.1. Metabolic alkalosis

If the patient shows symptoms of metabolic alkalosis with a HCO_3 > 30mmol/L the following should be followed:

- Continue diuretics per protocol.
- Add acetazolamide 500mg IV 6h until resolved

6.2.4.2. Hypernatremia

If the patient has hypernatremia with Na^+>150, the following should be followed:

- Continue diuretics per protocol.
- Add NG water or 5% dextrose according to local policy until resolved.
- Consider increasing thiazide dose.

6.3. Control – standard care

Patients will be prescribed fluids according to usual care, at the discretion of the treating clinicians.

- Intravenous drugs will be given in standard dilutions according to local ICU policy and maintenance fluid will be given as directed by the treating clinician.
- Fluid boluses will be given as deemed clinically indicated and sites will be encouraged to follow the Best Practice Statement in the Surviving Sepsis Campaign international guidelines that “fluid administration is continued as long as hemodynamic factors continue to improve… [applying] a fluid challenge technique”.

Fluid balance targets will be set by the treating clinicians and diuretic use will be allowed as clinically indicated.

7. Revision History

SSPM Ref.	Date Effective	Reason for update (page and section of change)
v1.0	10 Nov 2023	First version

8. Attachment A - Intervention flow chart