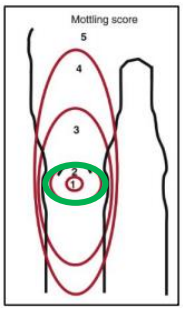
Fluid Intervention Summary

Day 1 - 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 (mottling applies to the extremities too, not only the knee)
- 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)

Re-assess patient- after bolus administration, re-assess - have the original signs of hypovolaemia listed above been resolved?

Yes – if signs of hypovolaemia above have been resolved, there is no indication for further IV fluid.

No - signs of possible hypovolaemia remain. Further fluid boluses may be given. 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 normalities 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.
Intravenous drugs will be given in the smallest acceptable volumes.

Day 2-5 – Deresuscitation - On day 2-5 patients will be assessed for fluid overload and cardiovascular stability:

- **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).
- **Cardiovascular stability** is defined as norepinephrine requirement <0.2 mcg/kg/min and not increasing, AND no signs of hypovolaemia (four points listed above)

Fluid overload + cardiovascular stability = **give deresuscitation**	No fluid overload OR cardiovascular instability = **continue with conservative fluid therapy** and reassess patient next day

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

- Oral indapamide 5mg daily (Or any equivalent thiazide diuretic e.g., metolazone 5mg OD / bendroflumethiazide 5mg OD)
- Furosemide 0.25mg/kg IV bolus (to the nearest 10mg, maximum 40mg)
- Furosemide infusion starting at 5mg/hr, titrated between 2-20mg/hr.

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 deresuscitation 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.

Frequently asked questions

Does you patient require IV glucose?

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. You only need about 50g of glucose a day to prevent ketosis, which works out at 250mL of 20% dextrose in 24h, assuming no other calorie intake. Bottom line: 15-20ml/h of 20% dextrose will work well (or even 30ml/hr of 10% dextrose which is more suitable for peripheral infusion if no central line present).

Is the patient showing symptoms of metabolic alkalosis?

If the patient shows symptoms of metabolic alkalosis with a HCO3 > 30mmol/L the following should be followed:

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

Does the patient have 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.

Does the patient feel 'shocky'?

If the patient is showing signs of hypovolemia, i.e. noradrenaline is going up or any of the other signs of objective hypovolemia listed on page one, they should receive a bolus of 250mls. If this resolves the hypovolemia partially, this may be repeated. However, the patient should be reassessed the next day for fluid overload and cardiovascular stability as above.

Can Plasmalyte crystalloid be used in the fluid intervention as a type of isotonic crystalloid?

Yes, please use your standard crystalloid solution for fluid boluses. Only give the boluses according to the criteria that suggest hypovolaemia**.**

How should you integrate cardiac output monitoring into the conservative fluid management strategy?

If a cardiac output monitor is used, the indications for fluid boluses remain unchanged. If desired, a change in stroke volume >10% in response to a fluid bolus may be used to predict further fluid responsiveness. However, the defined indications for fluid boluses remain the same i.e. skin mottling beyond the area of the kneecap, BP not maintained despite up-titration of vasoactive drugs, lactate >=3mmol/L, or UO <0.25ml/kg/h (on day 1 only). To put it a different way, the goal is to ensure adequate perfusion, not to eliminate fluid responsiveness.

What if the treating clinician does not wish to follow the conservative fluid flowchart?

We would advise to follow the fluid trial flowchart/fluid manual where possible. If the treating clinician does not wish to follow the plan e.g.: patient is stable, please record the decision and reason why in the patient notes so this is clear for monitoring purposes.

What needs to be reported as a protocol deviation in the fluid domain? Does every fluid bolus that is given in the conservative arm in patients who don't meet the criteria for the fluid intervention need to be reported?

We are not centrally monitoring deviations for fluids. Sites should monitor themselves and (re)educate local clinicians as needed. The study team will be monitoring adherence by looking at diuretic use if fluid balance is positive on days 2-5, while noradrenaline is <0.2.

Is it safe to give diuretics in patients who are on noradrenaline or who have acute kidney injury?

In numerous large trials, more conservative fluid strategies, including this one, have been shown to be safe. Conservative fluid administration or diuretics, as described in this protocol, do not worsen cardiovascular stability or kidney function. This protocol does not require clinicians to give diuretics if there is a real likelihood of hypovolaemia – if there is objective evidence of hypovolaemia, the approach above allows for corrective measures to be taken.