

COVID-19 Pandemic Version

Introduction

Continuous Renal replacement Therapy (CRRT) is a commonly initiated treatment on the ICU. Indications for CRRT include Acute Kidney Injury (AKI) with metabolic acidosis, hyperkalaemia, excessive uraemia or fluid overload, End Stage Renal Failure (ESRF) in patients who are unable to receive intermittent dialysis and the treatment of certain poisonings (where additional clearance of the poison is provided via the filter).

These guidelines collate previous trust guidelines regarding the delivery of CRRT in the ICU as well as including new guidelines relating to the use of Regional Anticoagulation with Citrate (RAC). They refer specifically to the General Intensive Care Units (and do not cover practice on LITU).

Following international guidelines (KDIGO clinical practice guideline for acute kidney injury, 2012) RAC should be considered as first choice for anticoagulation for most patients. The first section of these guidelines describe the use of CRRT with RAC. The second section of the guidelines considers the delivery of CRRT in patients not receiving RAC (including CRRT without anticoagulation). The final section outlines universal considerations regardless of method of anticoagulation.

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Regional Anticoagulation with Citrate (RAC)

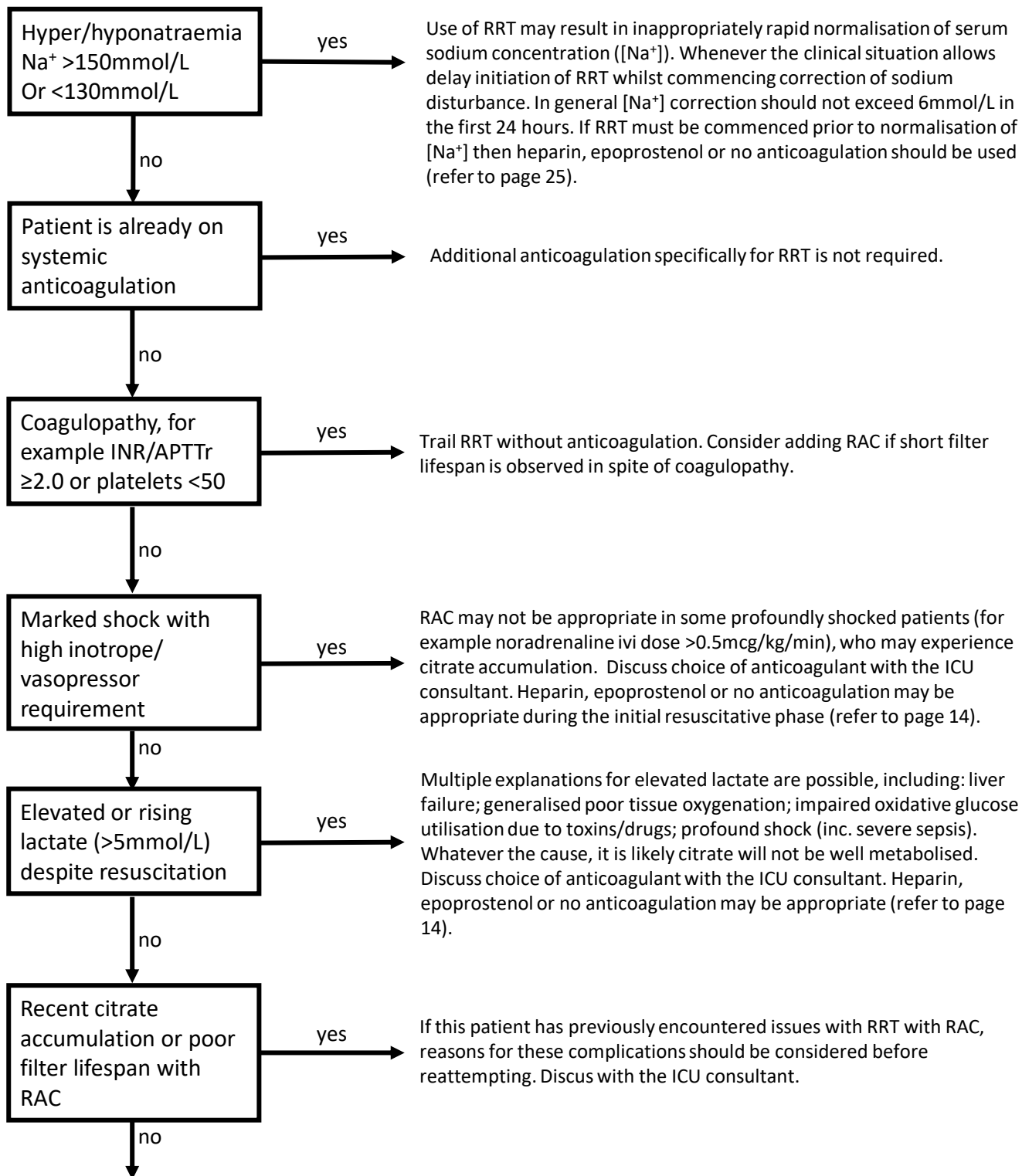
International guidelines (KDIGO clinical practice guideline for acute kidney injury, 2012) recommend using RAC in preference to systemic anticoagulation with heparin as first line in patients receiving continuous Renal Replacement Therapy (RRT) for Acute Kidney Injury (AKI), unless contraindications to RAC are present. This is based on randomised controlled trial data that demonstrated advantages of RAC including: increased filter lifespan; fewer episodes of filter clotting; fewer episodes of major bleeding.

Citrate's anticoagulant effect arises from chelating ionised calcium when it is infused pre-filter (with calcium being an important cofactor in many reactions within the coagulation cascade). Some of the citrate is removed by the filter, whilst any citrate that returns to the patient is metabolised by the liver, muscle and kidneys in to bicarbonate. Additional calcium is added to the blood post-filter, to restore a normal ionised calcium level, which reverses the anticoagulant effect.

The most important potential adverse effects of RAC include: acid-base disturbances (both alkalosis and acidosis can occur); citrate accumulation; hypo/hypercalcaemia. Safe application of RAC requires monitoring for these complications and adjusting/terminating therapy as indicated.

As citrate can also bind to magnesium there is the potential for increased magnesium losses when using RAC. Theoretically this might result in an increased requirement for supplemental magnesium infusions in patient's receiving RAC, however observational data suggests this is only a minor risk. In patient's for whom tight control of magnesium levels are critical, increased frequency of blood sampling to check magnesium levels whilst patients are receiving RAC seems prudent.

Choice of anticoagulant



Regional Anticoagulation with Citrate

Setting up the system

Choose post-filter replacement fluid:
 $K^+ \geq 5.5\text{mmol/L}$ -> Hemosol B0 (K^+ free)
 $K^+ < 5.5\text{mmol/L}$ -> Pristasol 4 (K^+ 4mmol/L)

Set-up and prime circuit according to machine instructions.

Set-up calcium infusion pump.

Calculate the ideal body weight (IBW). The IBW will be used in all calculations.

Select and enter the desired treatment dose (total effluent dose).

Measure ionised $[Ca^{2+}]$ (on ABG) and select and enter the % calcium correction.

Aspirate both vas-cath ports and ensure they are aspirating effectively.

Connect the patient to the circuit.

Commence RRT with RAC

In addition you will require Prismocitrate (RAC and pre-filter replacement fluid) and Prismocal (dialysate solution).

Refer to figure 1 (page 05) which illustrates an overview of the circuit and the fluid solutions required. Prime with 2x 1000ml bags of 0.9% sodium chloride (the first bag should have 5000 units of heparin added – unless heparin is contraindicated).

Draw up 50ml of Calcium Chloride 14.7% in a 50ml syringe (50mmol of calcium /50ml). Connect the syringe to the calcium line (use standard 50ml syringe and dedicated Baxter giving set) and attach to the PrisMax machine, which will prime the line automatically.

Calculate the IBW based on the patient's height (if known) or ulnar length (if the patient's height is unknown). Round IBW to the nearest 10kg for treatment dose calculations.

The treatment dose will be selected by the ICU consultant. The PrisMax machines are pre-programmed for treatment doses of 24, 36, 44 and 60ml/kg/hr (for IBWs 50-90kg, rounded to the nearest 10kg). Details are listed in tables 1-4 (page 06).

The calcium correction aims to maintain ionised $[Ca^{2+}]$ between 1.0-1.3mmol/L. Unless pre-RRT ionised $[Ca^{2+}]$ is $< 1.0\text{mmol/L}$ or $> 1.3\text{mmol/L}$ set calcium correction to 100%. If ionised $[Ca^{2+}]$ is outside this range refer to table 5 (page 07).

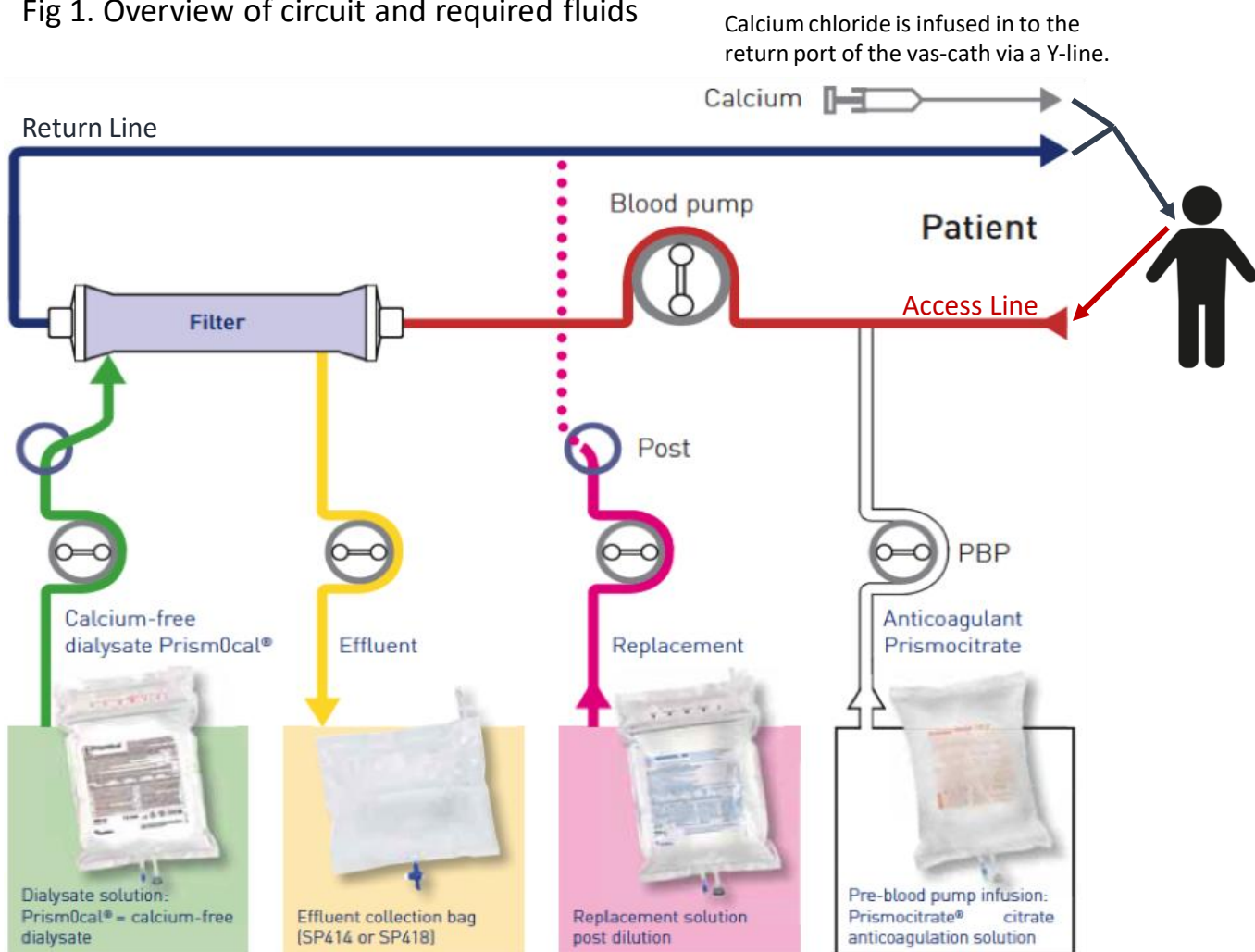
Aseptic Non-Touch Technique (ANTT) should be followed. Aspirate and discard 2ml from each lumen. Use a 20ml syringe to aspirate 20ml from each port. This should be performed in < 6 sec to simulate BFR of 200ml/min. The aspirated blood should be returned after aspiration.

The steps involved in connecting the patient to the circuit are detailed in figure 2 (page 07).

Monitor for effectiveness and safety.

Setting up the system

Fig 1. Overview of circuit and required fluids



	Prism0cal B22	Prismasol 4	Hemosol B0	Prismocitrate 18/0
Fluid type	Dialysate solution	Post-filter replacement fluid	Post-filter replacement fluid	RAC and pre-filter replacement fluid
Na ⁺	140	140	140	Na ⁺ 140
K ⁺	4	4	0	Cl ⁻ 86
Ca ²⁺	0	1.75	1.75	Citrate 18
Mg ²⁺	0.75	0.5	0.5	
Cl ⁻	120.5	113.5	109.5	
Lactate	3	3	3	
HCO ₃ ⁻	22	32	32	
Glucose	6.1	6.1	0	
(all mmol/L)				
Osmolality (mosmol/L)	296.4	301	287	Osmolality 244

Setting up the system

Treatment dose (total effluent dose)

Treatment dose is calculated based on ideal body weight (IBW) and expressed in ml/kg/hr.

IBW should be entered in to the PrisMax to the nearest 10kg (for example if IBW = 54.9kg then enter 50kg, and if IBW = 55.0kg enter 60kg). Always consider reducing the total effluent dose as soon as initial metabolic goals have been achieved (minimum dose is 24ml/kg/hr). When changing total effluent dose (up or down) in a patient established on RAC, change BFR, dialysate and post-filter replacement fluid rates (as per tables below), but leave PBP Cit at current dose.

$$\text{Total Effluent} = \text{PBP} + \text{Dia} + \text{Rep} + \text{PFR}$$

Table 1. Initial settings for total effluent dose 24ml/kg/hr

IBW (kg)	BFR ml/min	PBP Cit mmol/L	(PBP) ml/hr	Dia ml/hr	Rep ml/hr	Ci load
50	80	3.0	(800)	250	150	
60	80	3.0	(800)	500	150	9.1
70	80	3.0	(800)	800	150	8.1
80	80	3.0	(800)	800	300	7.6
90	90	3.0	(900)	900	400	8.4

Table 2. Initial settings for total effluent dose 36ml/kg/hr

IBW (kg)	BFR ml/min	PBP Cit mmol/L	(PBP) ml/hr	Dia ml/hr	Rep ml/hr	Ci load
50	80	3.0	(800)	800	250	7.8
60	90	3.0	(900)	900	300	8.7
70	110	3.0	(1100)	1100	350	10.9
80	120	3.0	(1200)	1200	400	11.9
90	140	3.0	(1400)	1400	450	14.2

Table 3. Initial settings for total effluent dose 44ml/kg/hr

IBW (kg)	BFR ml/min	PBP Cit mmol/L	(PBP) ml/hr	Dia ml/hr	Rep ml/hr	Ci load
50	90	3.0	(900)	900	350	8.6
60	110	3.0	(1100)	1100	450	10.6
70	130	3.0	(1300)	1300	500	12.8
80	150	3.0	(1500)	1500	550	15.1
90	160	3.0	(1600)	1600	700	15.9

Table 4. Initial settings for total effluent dose 60ml/kg/hr

IBW (kg)	BFR ml/min	PBP Cit mmol/L	(PBP) ml/hr	Dia ml/hr	Rep ml/hr	Ci load
50	120	3.0	(1200)	1200	500	11.5
60	150	3.0	(1500)	1500	600	14.7
70	170	3.0	(1700)	1700	700	16.8
80	200	3.0	(2000)	2000	800	20.3
90	220	3.0	(2200)	2200	900	22.6

- BFR: Blood Flow Rate (blood pump speed) – defaults to one tenth (in ml/min) of PBP (in ml/hr)
- PBP Cit: Concentration of citrate within the blood (mmol/L of blood)
- PBP: Pre Blood Pump (flow rate of citrate in ml/hr – calculated by machine when PBP Cit specified).
- Dia: Dialysate flow rate (in ml/hr).
- Rep: Post filter replacement fluid (haemofiltration/convective part of RRT in ml/hr).
- PFR: Patient Fluid Removal.
- Ci load: Calculated citrate load (in mmol/hr) based on haematocrit of 30% (should be <30mmol/hr).

Setting up the system

Calcium correction

Calcium is lost in the filter by dialysis or filtration. Calcium loss is proportional to the total effluent dose and the machine software can calculate the estimated calcium loss.

Supplemental calcium (in the form of calcium chloride) is added to the returning post-filter blood flow before it is returned to the patient, in order to prevent systemic hypocalcaemia and reverse the anticoagulant effect of RAC. The user must set the percentage of estimated lost calcium that should be added (calcium correction, expressed as %). If the patient's systemic ionised calcium concentration is within the target level (1.0-1.3mmol/L), then calcium correction should be set to 100%, i.e. the machine should replace exactly as much calcium as is expected to be lost.

Table 5. Initial calcium compensation setting at start of RRT

Systemic ionised [Ca ²⁺] (measured on ABG)	Initial calcium compensation
<1.0mmol/L	Medical team to establish cause of hypocalcaemia and consider calcium replacement. Ionised [Ca ²⁺] should be ≥1.0mmol/L for ≥6 hours before starting RRT with RAC.
1.0-1.3mmol/L	100%
>1.3mmol/L	90%

Patient connections

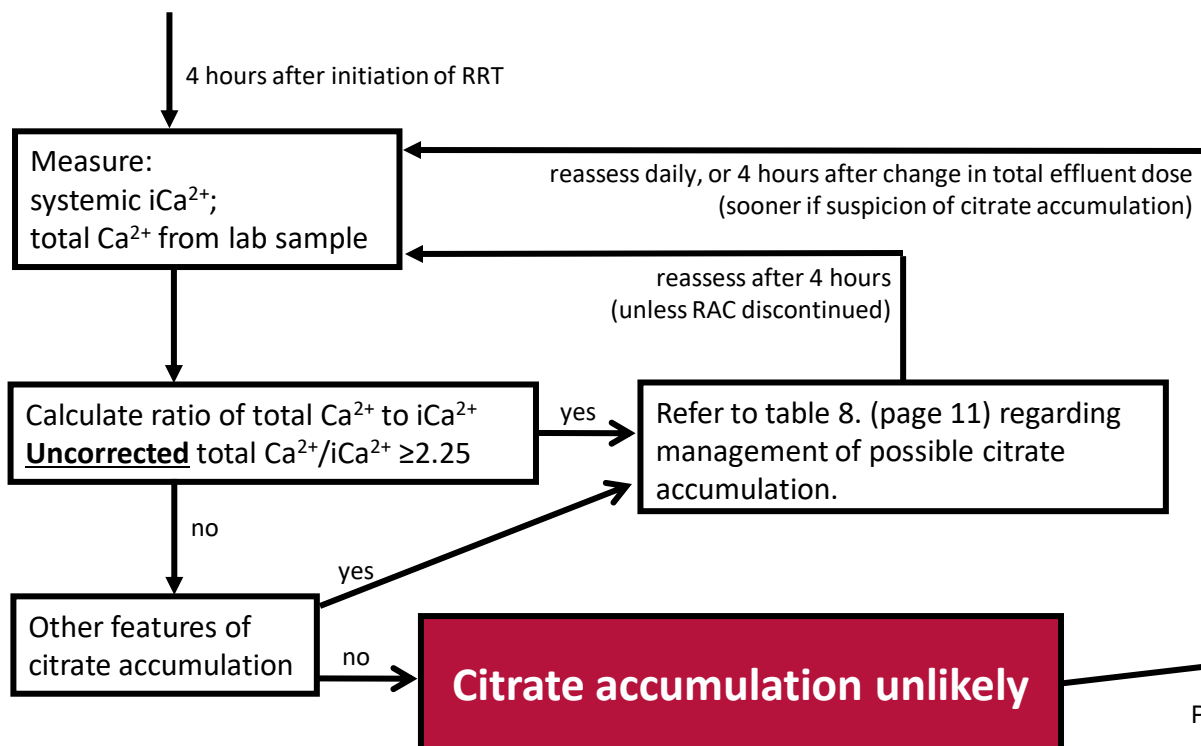
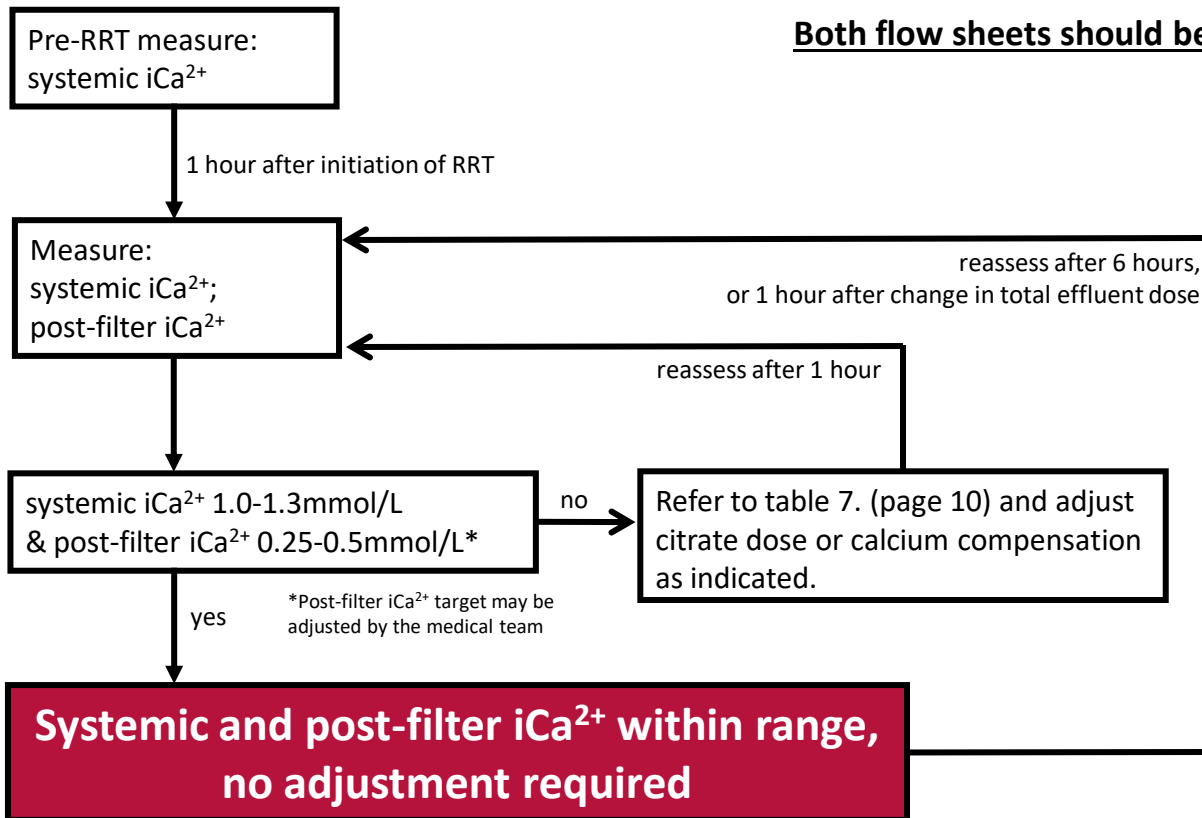
Fig 2. circuit connections



- Clamp ALL **Y-line** connections, **red access line**, **effluent line** and **blue access line** (as per machine instructions).
- Disconnect **red access line** from **Y-line** and connect to **access port** of vas-cath.
- Disconnect **blue return line** from **effluent bag** and connect to free port of **Y-line**.
- Disconnect **effluent line** from **Y-line** and connect to **effluent bag**. Keep free port on **Y-line** sterile after disconnection.
- Connect calcium line to free port of **Y-line**.
- Disconnect **Y-line** from priming solution bag and connect **Y-line** to **return port** of vas-cath.

Routine monitoring

Both flow sheets should be followed



Routine monitoring

Monitoring systemic and circuit calcium

Three different calcium measurements will need to be made at regular intervals whilst RRT with RAC is in operation to ensure adequate levels of anticoagulation, as well as patient safety:

Post-filter ionised Ca²⁺

The concentration of free calcium in the blood immediately after the blood has left the filter. This reflects the degree of anticoagulation with RAC. The target range is 0.25-0.5mmol/L (the range may be adjusted by the medical team, a lower target may be set if there has been premature filter clotting despite having achieved the post-filter iCa²⁺ target). Levels above the target range indicate inadequate anticoagulation, whilst levels below the target range indicate unnecessarily excessive citrate administration. This sample is taken with a standard blood gas syringe from the post-filter blue sampling port.

Systemic ionised Ca²⁺

The concentration of free calcium in the patient's blood. Monitoring systemic ionised Ca²⁺ is essential to ensure patient safety, and avoid hyper/hypocalcaemia. The target range is 1.0-1.3mmol/L. Levels below the target range suggest calcium replacement is inadequate or that citrate accumulation may be occurring (citrate-calcium complex not metabolised, so calcium not liberated). The sample is taken with a standard blood gas syringe from the patient's arterial line.

Ratio of systemic uncorrected total Ca²⁺ to ionised Ca²⁺

This is calculated by taking the uncorrected Ca²⁺ concentration from a laboratory biochemistry sample and dividing it by the systemic ionised Ca²⁺ level (taken from the patient's ABG, and drawn at the same time as the biochemistry sample). Usually >44.4% of the total calcium is free (ionised), which will result in a ratio of <2.25. An elevated ratio reflects a lower proportion of the total calcium being free, which may be due to citrate accumulation within the patient.

Table 6. Timing of post-filter and systemic calcium measurements

Calcium measurement	After initiation of RRT or change in total effluent dose	Once RRT established and measurement within target range
Post-filter iCa ²⁺	1 hourly until within target range	6 hourly
Systemic iCa ²⁺	Before start of RRT, then 1 hourly until within target range	6 hourly
Uncorrected total Ca ²⁺ / iCa ²⁺ (drawn simultaneously)	4 hourly until within target range	Daily, or 4 hourly if signs of citrate accumulation

Optimisation of anticoagulation

Post-filter iCa^{2+} (and systemic iCa^{2+}) are measured regularly in order to ensure adequacy of anticoagulation (and patient safety). Post-filter iCa^{2+} is corrected by adjusting the dose of citrate added to the pre-filter blood (i.e. by adjusting the dose of amount of Prismocitrate added – PBP).

Citrate dose = (citrate flow rate x citrate concentration) / blood flow rate

The concentration of citrate in Prismocitrate is fixed at 18mmol/L. Citrate flow rate = PBP. Blood flow rate is adjusted automatically by the machine whenever citrate dose or PBP are altered.

For all settings (tables 1-4) the initial citrate dose (concentration in pre-filter blood) is 3mmol/L.

Systemic iCa^{2+} is corrected by adjusting the % calcium correction. When % calcium correction is altered the machine will automatically adjust the rate of calcium chloride infusion in the blood returning to the patient.

Table 7. Management of post-filter and systemic iCa^{2+} levels

		Post-filter iCa^{2+}		
		<0.25mmol/L	0.25-0.5mmol/L	>0.5mmol/L
Systemic iCa^{2+}	<1.0mmol/L	Decrease citrate dose by 0.5mmol/L of blood.*	Increase calcium compensation by 10%.	Increase citrate dose by 0.5mmol/L of blood.* AND Increase calcium compensation by 10%.
	1.0-1.3mmol/L	Decrease citrate dose by 0.5mmol/L of blood.*	Targets achieved. Maintain current settings.	Increase citrate dose by 0.5mmol/L of blood.*
	>1.3mmol/L	Decrease citrate dose by 0.5mmol/L of blood.* AND Decrease calcium compensation by 10%.	Decrease calcium compensation by 10%.	Decrease calcium compensation by 10%. Recheck post-filter iCa^{2+} after 1 hour. If post-filter iCa^{2+} remains above target THEN increase citrate dose by 0.5mmol/L of blood.*

*It is important to appreciate that as anticoagulation and replacement fluid are delivered as one (prismocitrate), adjusting the dose of citrate will alter the total effluent dose. Decreasing citrate dose will decrease total effluent dose (by ~7% per 0.5mmol/L of blood, greater if IBW 50-60kg and total effluent dose 24ml/kg/hr). Increasing citrate dose will increase total effluent dose (by ~7% per 0.5mmol/L of blood, greater if IBW 50-60kg and total effluent dose 24ml/kg/hr).

Management of suspected citrate accumulation

The ratio of systemic uncorrected total Ca^{2+} to iCa^{2+} should be measured regularly (from simultaneously drawn samples) in order to monitor for evidence of citrate accumulation within the patient. Citrate may accumulate due to impaired ability of the patient to metabolise citrate. Citrate is an acid and its accumulation may lead to or worsen metabolic acidosis. As citrate binds to calcium as it accumulates it will lead to a fall in free (ionised) calcium but a rise in total calcium (bound and unbound calcium).

The ideal ratio is <2.25 . A ratio of $2.25-3.0$ may be temporarily accepted if metabolic acidosis is improving and other parameters are stable.

Additional signs of citrate accumulation:

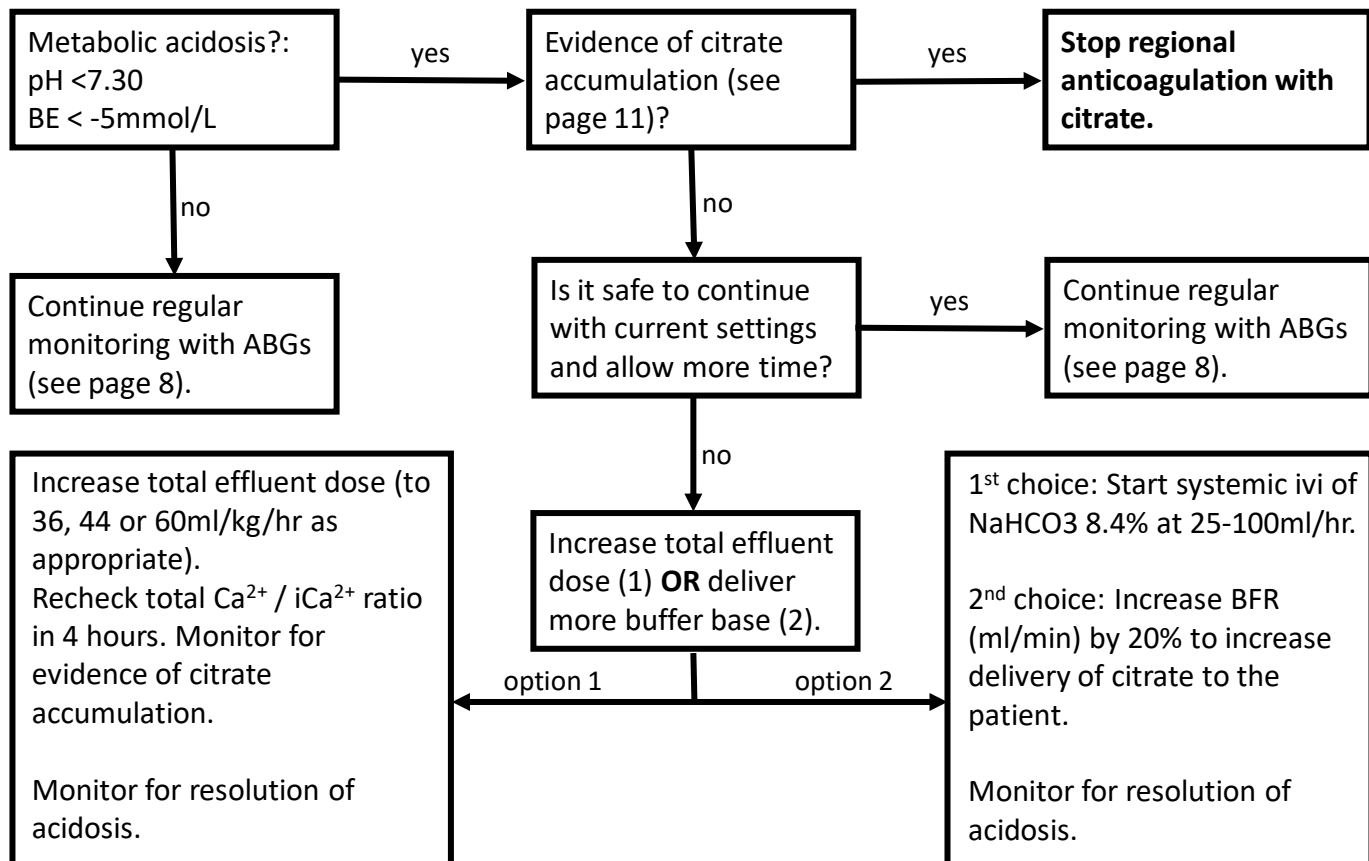
- Calcium compensation has been progressively increased to $\geq 140\%$ and/or systemic iCa^{2+} levels remain $<1.0\text{mmol/L}$ (as measured on hourly ABGs).
- Newly developed or worsening metabolic acidosis during RRT which is unexplained by the underlying disease process.
- Lactate rises rapidly or lactate $>5\text{mmol/L}$.
- Systemic uncorrected total Ca^{2+} $>3\text{mmol/L}$.

Ratio: $\frac{\text{Uncorrected total Ca}^{2+}}{\text{iCa}^{2+}}$

Table 8. Management of suspected citrate accumulation

Ratio	Action
<2.25	<p>Target achieved. Continue to monitor daily.</p> <p>Consider possibility of citrate accumulation.</p> <p>Accept this ratio initially if metabolic acidosis has resolved or is improving significantly, lactate is stable, systemic iCa^{2+} is stable and calcium compensation is stable. If these parameters are not met assume citrate accumulation and stop regional anticoagulation with citrate.</p>
$2.25-3.0$	<p>If RAC continues reduce citrate dose by 0.2mmol/L of blood every hour, targeting a post-filter iCa^{2+} of $0.4-0.5\text{mmol/L}$ (continue to decrease citrate dose in a stepwise fashion until post-filter iCa^{2+} within this new range).</p> <p>AND</p> <p>Recheck ratio of systemic uncorrected total Ca^{2+} to iCa^{2+} after 4 hours. If ratio remains $2.25-3.0$ after 4 hours consider either increasing dialysate flow rate by 50% or stopping regional anticoagulation with citrate.</p> <p>If ratio remains $2.25-3.0$ for ≥ 12 hours then stop regional anticoagulation with citrate.</p>
>3.0	<p>Stop regional anticoagulation with citrate.</p>

Management of metabolic acidosis

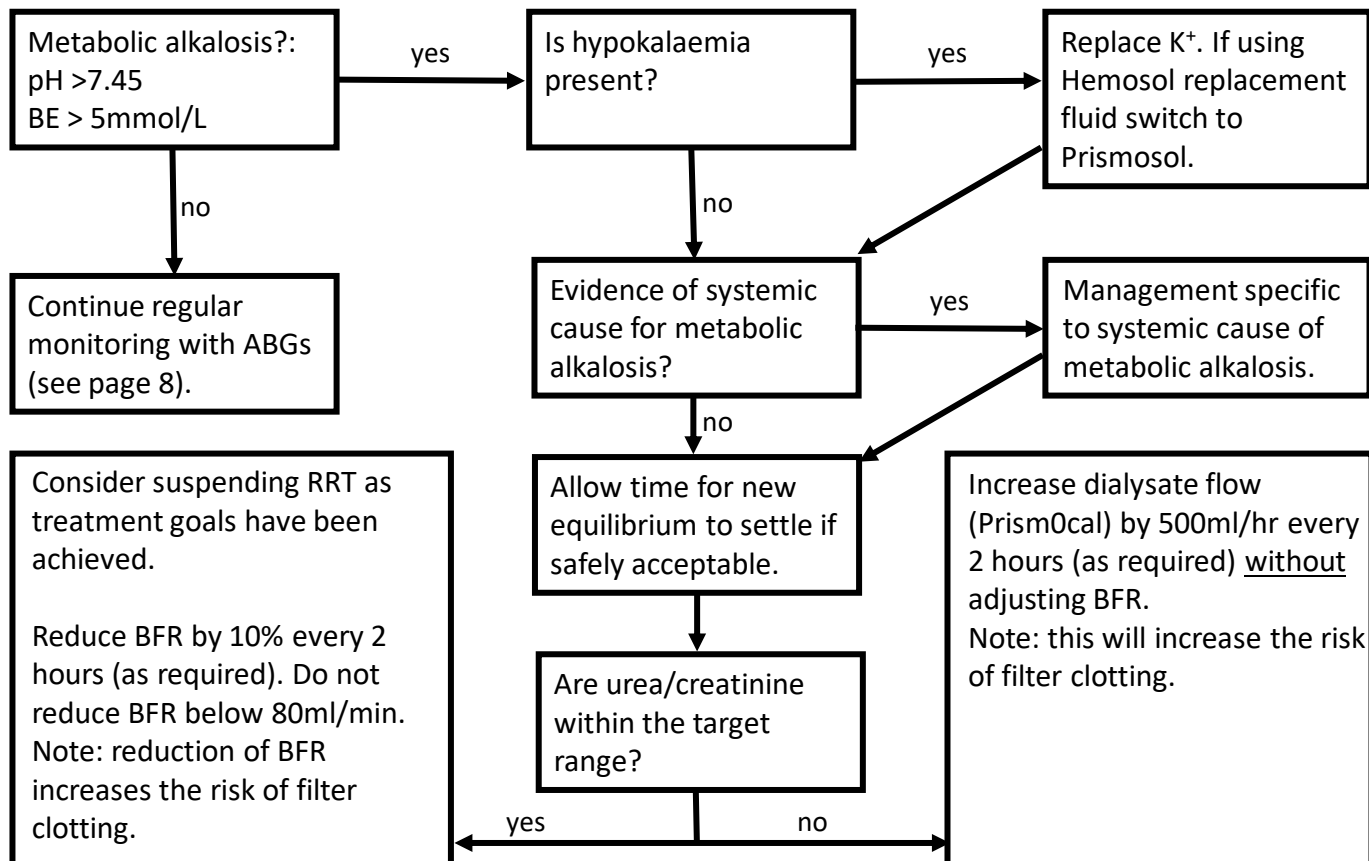


When metabolic acidosis (pH <7.30, BE <-5mmol/L) newly arises or worsens during RRT consider and establish the most likely cause.

Metabolic acidosis during RRT has one or several of the following causes:

- The underlying disease process still drives the production of acids (lactate, ketones).
ACTION: Manage the underlying cause **AND** consider increasing the total effluent dose.
- The process driving metabolic acidosis is settling but clearance of acids by RRT is slow (uraemic acids, toxins, lactate, ketones).
ACTION: Allow more time if safely possible **OR** consider increasing the total effluent dose.
- RRT does not return enough buffer base (bicarbonate or citrate) to the patient.
ACTION: Systemic administration of NaHCO₃ 8.4% at 25-100ml/hr (first choice)
OR Increase the citrate delivery to the patient by increasing the BFR as long as citrate accumulation is not suspected (second choice, as there may be uncertainty as to whether there is citrate accumulation or not).
- Citrate is not sufficiently metabolised by the patient (i.e. citrate accumulation).
ACTION: Refer to page 11 ('Management of suspected citrate accumulation').

Management of metabolic alkalosis



When metabolic alkalosis (pH >7.45, BE > 5mmol/L) newly arises or worsens during RRT consider and establish the most likely cause.

Metabolic alkalosis during RRT has one or several of the following causes:

- Systemic causes: hypokalaemia; post-hypercapnoea alkalosis; diuretics used before RRT; vomiting and gastric aspirations (unlikely if patient receiving a proton-pump inhibitor); primary hyperaldosteronism.

ACTION: Replace K⁺ as required **AND** diagnose systemic causes.

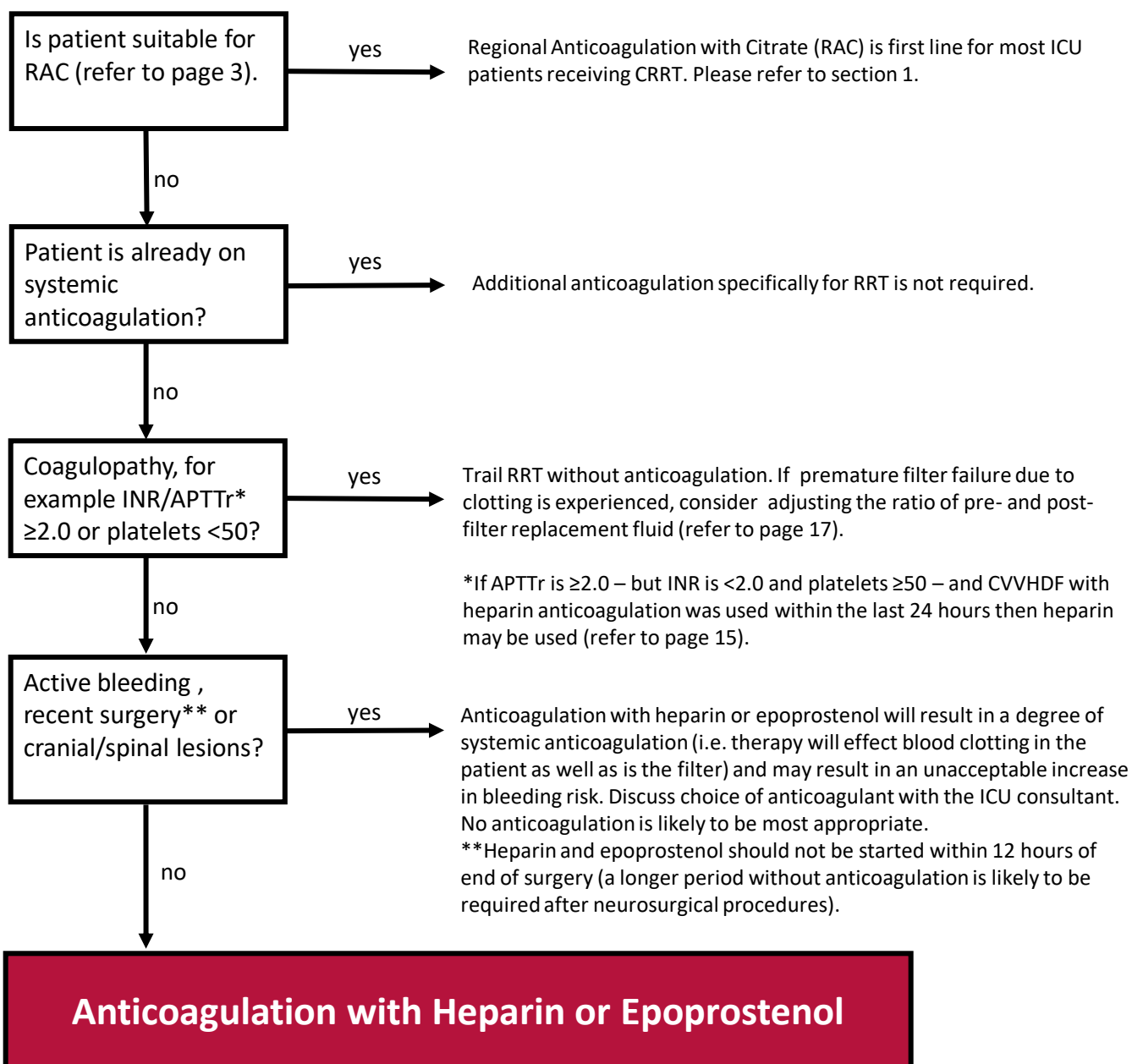
- Citrate delivery too high.

ACTION (if urea/creatinine are within target range): consider suspending/discontinuing RRT (as RRT goals targets have been achieved) **OR** reduce BFR by 10% every 2 hours (to reduce citrate delivery to the patient – note: reduction in BFR increases the risk of the filter clotting and BFR should not fall below 80ml/min).

ACTION (if urea/creatinine remain above the target range): increase the total effluent dose by increasing dialysate flow in steps of 500ml/hr without increasing BFR (this will increase the removal of citrate within the filter – note: increase in dialysate flow without an increase in BFR increases the risk of circuit clotting).

Alternative Anticoagulation

For patients in whom RAC is not appropriate CRRT can be performed either without any specific additional anticoagulation, or with an alternative anticoagulant such as heparin or epoprostenol.



Heparin acts as an anticoagulant by binding to and activating antithrombin III, which in turn inhibits thrombin and other clotting factors. Epoprostenol is a synthetic analogue of prostacyclin and acts as an anticoagulant by reversibly inhibiting platelet aggregation. Even when given as part of CRRT both of these methods of providing anticoagulation will have effects on systemic coagulation (i.e. within the patient). Discuss choice of anticoagulant (heparin or epoprostenol) with the ICU consultant.

Heparin

Determine if a bolus dose of heparin should be given.

If the APTTr is ≥ 2.0 a bolus dose of heparin should not be given.

If the APTTr is < 2.0 then usual practice on GICU is that a bolus dose of 2000 iu heparin should be given (at the discretion of the ICU consultant).

Determine the infusion dose of heparin (via circuit).

Administer 2000 iu of heparin in to the red port of the circuit prior to connecting the circuit to the patient.

**For all heparin doses use actual body weight (ABW).
For patients $> 120\text{kg}$, use the weight 120kg in calculations.**

Has the patient received CVVHDF with heparin in the last 24 hours?

no

Commence heparin (via the circuit) at 5 iu/kg/hr.

yes

Did the last circuit last > 24 hours?

yes

Recommence heparin at the most recent dose.

no

Increase the most recent heparin dose by 2.5 iu/kg/hr*.
Do not exceed 20 iu/kg/hr.
*If filter clotted within 6 hours of a dose reduction then the infusion should be started at the pre-reduction dose.

Check APTTr after 6 hours.

Measure APTTr.

< 2.0	2.0 - 2.8	2.9 - 3.2	> 3.2
Optimum. No change to heparin dose.	Reduce heparin dose by 150 iu/hr.	Stop heparin for 30 minutes. Then restart at half the previous dose.	Stop heparin for 60 minutes. Then restart at half the previous dose.

Check APTTr after 24 hours.

Check APTTr after 6 hours.

Discontinue heparin if patients develop INR ≥ 2.0 or platelets < 50 , whilst therapy is ongoing

Epoprostenol

Epoprostenol is an alternative to heparin in patients who cannot receive RAC. The dose of epoprostenol is 1-10ng/kg/min (based on ideal body weight). Epoprostenol can be used instead of heparin or (when premature circuit clotting occurs) alongside heparin.

The dose of epoprostenol is titrated based on observed circuit lifespan. The usual starting dose is 2.5ng/kg/min. No specific monitoring is required and the dose continues at the same rate unless premature clotting occurs, in which case it can be up titrated, usually in steps of 2.5ng/kg/min (up to a maximum dose of 10ng/kg/min).

Side effects include flushing, hypotension and tachycardia, and the dose can be reduced (or therapy discontinued) if these symptoms are noted and attributed to epoprostenol.

Epoprostenol is always made up to a concentration of 2mcg/ml.

$$\text{Infusion Rate (ml/hr)} = \text{Desired Dose (ng/kg/min)} \times \text{IBW (kg)} \times 0.03$$

Table 9. Example infusion rates (ml/hr) required to achieve desired epoprostenol dose

IBW (kg)	2.5 ng/kg/min	5.0 ng/kg/min	7.5 ng/kg/min	10.0 ng/kg/min
50	3.8 ml/hr	7.5 ml/hr	11.3 ml/hr	15.0 ml/hr
60	4.5 ml/hr	9.0 ml/hr	13.5 ml/hr	18.0 ml/hr
70	5.3 ml/hr	10.5 ml/hr	15.8 ml/hr	21.0 ml/hr
80	6.0 ml/hr	12.0 ml/hr	18.0 ml/hr	24.0 ml/hr
90	6.8 ml/hr	13.5 ml/hr	20.3 ml/hr	27.0 ml/hr

Setting up the system

Treatment dose (total effluent dose)

Treatment dose is calculated based on ideal body weight (IBW) and expressed in ml/kg/hr. Always consider reducing the total effluent dose as soon as initial metabolic goals have been achieved. At King's the most commonly delivered total effluent doses are: 24ml/kg/hr; 36ml/kg/hr; 44ml/kg/hr; 60ml/kg/hr. Refer to page 20 for details on dose selection.

Selecting ratios of dialysate and replacement fluid

When using Continuous Veno-Venous HaemoDiaFiltration (CVVHDF) to provide CRRT fluid is added to the circuit in three locations: pre-filter replacement fluid (added to patients blood); dialysate (runs on the other side of the filter membrane to the patients blood); post-filter replacement fluid (added to the patients blood).

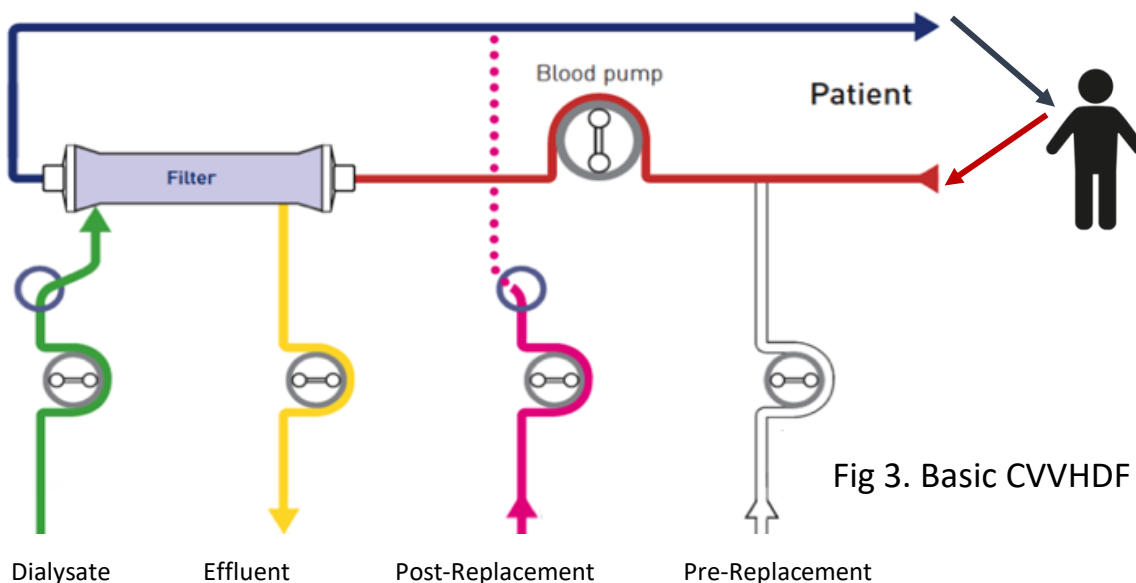


Fig 3. Basic CVVHDF configuration

The desired total effluent dose should be calculated, then divided between dialysate and replacement fluid.

If no anticoagulation is being used dialysate should be 50% of total effluent, whilst pre-replacement and post-replacement should both be 25% of total effluent. If heparin or epoprostenol are being used then dialysate should be 50% of total effluent, with pre-replacement being 16.7% and post-replacement being 33.3%.

If premature filter clotting occurs then proportion of the replacement fluid that is delivered pre-filter can be increased (whilst reducing the proportion that is delivered post-filter, and maintaining the same proportion that is dialysate). For example if no anticoagulation is used and premature clotting occurs change the delivered pre- and post-replacement fluids to 33% and 17% of the effluent dose respectively. If heparin or epoprostenol are being used and premature clotting occurs change the delivered pre- and post-replacement fluids to 25% and 25% of the effluent dose respectively.

COVID-19 Pandemic Version

Setting up the system (during the COVID-19 pandemic)

The following pages detail changes to the protocol specifically designed to counter the anticipated imbalance between demand for CRRT and equipment to provide CRRT during the COVID-19 pandemic. The intention is to maximise the use an individual patient gets from the filter for a given period of time, as it is expected rotating filters between patients will become necessary.

- **The tip of the vas-cath should be placed such that it lies as close as possible to the right atrium (without resting within the right atrium). When using the right internal jugular vein or the right subclavian vein a 16cm vas-cath will be appropriate for most patients. When using the left internal jugular vein, either femoral vein or the left subclavian vein a 20cm vas-cath should be used.**
- **As always ensure that 20ml of blood can be rapidly aspirated from both lumens (aspirate 20ml in less than 6 seconds).**
- **When the number of available CRRT machines exceeds the requirement for machines then commence the patient on 20ml/kg/hr, 36ml/kg/hr or 44ml/kg/hr depending on the degree of metabolic derangement (see tables 10-12, page 19).**
- **Whenever possible reduce the exchange to 20ml/kg/hr to reduce the strain on the filter.**
- **Higher doses of CRRT (>44ml/kg/hr) may be required in specific clinical settings (such as acute liver failure) and may be selected at the discretion of the ICU consultant.**
- **When the number of available CRRT machines is less than the number of patients requiring CRRT use a high total effluent dose (44ml/kg/hr, see table 12, page 19). After 8 hours – if the machine is required for another patient – the circuit can be ‘washed back’ to return the patients blood.**
- **Upon completing 8 hours at 44ml/kg/hr recheck the patient’s U&Es (to ensure adequate solute removal) and phosphate concentration (as phosphate may need to be topped up).**

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Selecting ratios of dialysate and replacement fluid

The following tables give examples of approximate starting rates of dialysate, and pre-filter and post-filter replacement fluid, for a variety of ideal body weights for the most commonly used total effluent doses used at King's, **for a patient receiving anticoagulation other than RAC** (i.e. either heparin, epoprostenol or systemic anticoagulation).

IBW should be entered in to the PrisMax to the nearest 10kg (for example if IBW = 54.9kg then enter 50kg, and if IBW = 55.0kg enter 60kg).

$$\text{Total Effluent} = \text{Pre} + \text{Dia} + \text{Post}$$

Table 10. Example settings for total effluent 20ml/kg/hr

IBW (kg)	BFR ml/min	Pre ml/hr	Dia ml/hr	Rep ml/hr	Tot ml/hr
50	200	175	750	75	1000
60	200	210	900	90	1200
70	200	245	1050	105	1400
80	200	280	1200	120	1600
90	200	315	1350	135	1800

Table 11. Example settings for total effluent 36ml/kg/hr

IBW (kg)	BFR ml/min	Pre ml/hr	Dia ml/hr	Rep ml/hr	Tot ml/hr
50	200	300	1350	150	1800
60	200	360	1620	180	2160
70	200	420	1890	210	2520
80	200	480	2160	240	2880
90	200	540	2430	270	3240

Table 12. Example settings for total effluent 44ml/kg/hr

IBW (kg)	BFR ml/min	Pre ml/hr	Dia ml/hr	Rep ml/hr	Tot ml/hr
50	250	400	1650	150	2200
60	250	480	1980	180	2640
70	250	560	2310	210	3080
80	250	640	2640	240	3520
90	250	720	2970	270	3960

If there is a shortage of CRRT machines commence on 44ml/kg/hr total effluent dose and rotate machines between patients every 8 hours.

Check U&Es/[Phosphate]

Total effluent >44ml/kg/hr only with consultant approval:

- BFR: 250ml/min
- PBP: 17% of total effluent dose
- Dia: 75% of total effluent dose
- Rep: 8% of total effluent dose

BFR: Blood flow rate (in ml/min)
 Pre: Pre-dilution (ml/hr)=PBP (Pre Blood Pump)
 Dia: Dialysate flow rate (in ml/hr).
 Rep: Post-filter replacement fluid (in ml/hr).
 Tot: Total effluent dose (in ml/hr)

Setting up the system

Choice of dialysate/replacement fluid (adjustments for potassium concentration)

When performing CVVHDF without RAC, the pre-filter replacement fluid, dialysate and post-filter replacement fluid should be identical (i.e. All three are the same fluid). Choice of fluid depends on the patient's potassium concentration (may be measured from arterial or venous blood gas).

When [K+] <5.5mmol/L use PrismaSol (potassium content 4mmol/L).

When [K+] ≥5.5mmol/L use Hemosol (potassium content 0mmol/L).

Priming the system

Regardless of method of anti-coagulation – unless heparin is contraindicated (for example in cases of proven or suspected Heparin Induced Thrombocytopenia) – heparin is used to prime the circuit. 2x 1000ml bags of NaCl 0.9% are used. The first bag should have 5000 iu of heparin added. The second bag should have no additives. In patients with a contraindication to heparin, both 1000ml bags of NaCl 0.9% should be used without any additives.

Blood pump speed

High blood pump speed preserves the integrity of the filter membrane by reducing the degree of protein deposition (albumin, immunoglobulins, fibrinogen) on to the membrane. Hence high blood pump speed reduces the risk of the filter clogging.

Set initial blood pump speed to 30ml/min.

Keep blood pump speed at 30ml/min until circuit is fully primed with blood.

Increase blood pump speed by 30ml/min every 10 seconds until target is reached.

Do not start ultrafiltration or dialysate flow until the target pump speed is reached (i.e. initially set total effluent at 0).

Total Effluent Dose	Target Blood Pump Speed
<3000ml/hr	200-250ml/min
3000-5000ml/hr	250ml/min
>5000ml/hr	250 to 300 ml/min

Total effluent dose selection

Numerous studies have compared different CRRT dosing strategies, and no single strategy has been consistently demonstrated to be superior. Higher total effluent doses may lead to over-clearance of medications (including antibiotics), nutrients and electrolytes (including hypokalaemia and hypophosphataemia). There may also be a risk (debated) of disequilibrium syndrome* if plasma concentrations of urea, creatinine and other osmotically active substances fall too rapidly.

For patients with severe metabolic acidosis or hyperkalaemia, or poisoning with renally excreted drugs a starting total effluent dose of 44ml/kg/hr (IBW) seems appropriate. A lower starting dose (24-36ml/kg/hr IBW) are likely to be adequate in patients with mild or no metabolic acidosis or hyperkalaemia.

Consider reducing the total effluent dose once pH and potassium concentrations have normalised. Consider reducing the dose to 24ml/kg/hr once target urea and creatinine have been reached.

Fluid removal

A daily fluid balance target and/or hourly fluid removal rate should be set by the medical team.

The hourly fluid removal rate should ideally be limited to ≤ 200 ml/hr (as high fluid removal rates may lead to cardiovascular instability, and may cause premature filter clotting or clogging). Rates >200 ml/hr are rarely indicated and should be reviewed frequently. Maximal recommended rate is 400ml/hr (for brief periods only).

Filtration Fraction (FF)

Filtration Fraction (FF) refers to the proportion of plasma flow that is filtered. FF should remain $\leq 25\%$ to maintain filter patency.

$FF = \text{Ultrafiltration rate} / \text{Plasma flow rate}$

Ultrafiltration rate = Fluid removal rate + replacement fluid rate (assuming 100% of replacement fluid is delivered post-filter)

Plasma flow rate = Blood pump speed * (1 – haematocrit)

Actions to consider if FF is $>25\%$:

- Increase blood pump speed (if using anticoagulant other than RAC – or no anticoagulant – and blood pump speed is below the target).
- Reduce total effluent dose (and hence reduce fluid replacement).
- Reduce fluid removal from the patient.

*Disequilibrium syndrome is a rare but serious complication of renal replacement, where patient's develop neurological symptoms (such as restlessness, headache, confusion and ultimately coma) during/following RRT. It is believed to be caused by fluid shifts across the blood-brain-barrier in patients undergoing rapid clearance of osmotically active substances (such as urea). It most commonly complicates an initial dialysis session, where these shifts are likely to be greatest.

Circuit pressures

The PrisMax machine displays system pressures in the bottom left hand corner of the main screen.

Access and return pressures

The access pressure is the pressure inside the circuit prior to the blood pump. The 'normal' range of pressures seen is -20mmHg to -150mmHg.

The return pressure is the pressure inside the circuit after the filter. The 'normal' range of pressures seen is +50mmHg to +200mmHg.

Trends in pressures over the course of treatment are more important than absolute values. An increasingly negative access pressure (or an initial access pressure more negative than -100mmHg) or an increasingly positive return pressure (or an initial access pressure more positive than +100mmHg) may represent insufficient flow through the vascath.

Causes:

- Kinking of the circuit or vascath.
- Clotting within the venous chamber, circuit or vascath.
- Sucking of the vascath outflow ('arterial' limb) against the vessel wall.

Actions:

- Inspect the circuit and tubing for kinks and unkink (as indicated).
- Adjust patient position to reduce risk of kinking (as indicated).
- Consider temporary reduction of blood pump speed (when not using RAC).
- Consider temporary reduction in fluid removal (or pausing fluid removal).
- Consider slight withdrawal or twisting of the vascath within the vein.
- Consider hypovolaemia as a possible cause of the vascath outflow sucking against the vessel wall.
- Consider whether or not the current vascath is adequately positioned to allow CRRT (there is a need to balance the risks to the patient of premature circuit failure against the risks of insertion of a new vascath).



Fig 4. Pressure display on PrisMax

Circuit pressures (continued)

Trans-Membrane Pressure (TMP)

A rise in the TMP represents filter 'clogging' (protein deposition on to the membrane). The maximal acceptable TMP varies depending on the filter used (the label on the side of the filter will state the maximal acceptable TMP for that device – Gambro ST150 maximum TMP is 450mmHg). Trends in TMP as well as absolute values should be observed. TMP should ideally remain <150mmHg.

Actions (for elevated/rising TMP – **when not using RAC**):

- Increase blood pump speed if possible (up to target speed – refer to page 19).
- Consider increasing dialysate flow rate.
- Consider reducing total effluent dose.
- Consider reducing fluid removal.

Pressure drop (ΔP)

A rise in ΔP represents clotting within the filter membrane. Trends in ΔP as well as absolute values should be observed. ΔP should ideally remain <150mmHg.

Actions (for elevated/rising ΔP – **when not using RAC**):

- Stop fluid removal temporarily.
- Increase proportion of replacement fluid that is given pre-filter.
- Consider reducing total effluent dose.
- Consider anticoagulation regime (discuss with the medical team, is there scope to commence anticoagulation in patients not receiving any, to give a bolus of heparin or add in epoprostenol).

**When considering circuit pressures the key value to remember is 150mmHg.
Return pressure, TMP and ΔP <150mmHg. Access pressure >-150mmHg.**

Circuit lifespan

The maximum lifespan of the CRRT circuit is 120 hours. The circuit will alarm after 72 hours to say that the circuit has expired. This can be over ridden as long as the TMP and ΔP are acceptable.

VTE prophylaxis

General guidance for VTE prophylaxis for patients admitted to critical care can be found in the protocol 'Prevention of venous thromboembolism in patients admitted to critical care units'.

Patients with eGFR <30ml/min or on CRRT should receive subcutaneous unfractionated heparin (UFH) unless contraindicated (patient actual body weight <100kg give 5000 units 12 hourly, patient actual body weight ≥100kg give 5000 units 8 hourly). Relative contraindications to pharmacological VTE prophylaxis with UFH are listed in the above protocol.

CRRT anticoagulation	VTE prophylaxis
No anticoagulation	Consider why no anticoagulation given, UFH likely to be contraindicated for the same reason
Systemic anticoagulation	Prophylactic UFH unnecessary if the patient is on effective systemic anticoagulation
Regional Citrate	UFH to be given unless specific contraindication applies
Heparin or epoprostenol	UFH to be given unless specific contraindication applies (if APTTr ≥2.0 and patient is receiving heparin via the filter then circuit heparin infusion dose requires adjustment – refer to page 15)

Table 14. Pharmacological VTE prophylaxis for different filter anticoagulation regimes

Heparin Induced Thrombocytopenia (HIT)

Patients with proven or suspected HIT with a high clinical risk will be systemically anticoagulated unless contraindicated (see the protocol 'The management of heparin induced thrombocytopenia'). Like all patients who are systemically anticoagulated no CRRT specific additional anticoagulation is required. The patient should receive no heparin, therefore the circuit should be primed with 2000ml of 0.9% sodium chloride.

In patients in whom the HIT antibody test is positive, but the clinical risk is low, the medical team may elect to not systemically anticoagulate the patient, but will still want to avoid giving heparin. In these patients RAC will be first line (see section 1 of this guideline). If RAC is contraindicated then other options for anticoagulating the CRRT circuit include epoprostenol (second line), danaparoid (third line) and argatroban (alternative choice). Choice of priming fluid will depend on choice of regional anticoagulant (refer to table 15, page 24).

Heparin Induced Thrombocytopenia (continued)

Anticoagulant	Prime	Dose	Reconstitution	Monitoring
Epoprostenol <i>Synthetic prostacyclin that inhibits platelet function</i>	2000ml 0.9% sodium chloride.	Continuous infusion via filter. 1-10ng/kg/min (ideal body weight). Titrate dose based on observed circuit lifespan. See page 16.	Epoprostenol 500mcg in 50mls diluent. Remove 50mls from a 250ml 0.9% sodium chloride infusion bag and add Epoprostenol 50ml. Final concentration 500mcg/250mls. Withdraw 100mcg in 50mls for each syringe. Change syringe every 12 hours. Remaining solution should be stored in the fridge for up to 24 hours and any remaining solution should be discarded.	No specific monitoring required.
Danaparoid <i>Inhibits the activated clotting factor Xa</i> <i>Each vial contains 750u/0.6ml</i>	Add 750-1500u of Danaparoid to 1000ml 0.9% sodium chloride. Followed by 1000ml 0.9% sodium chloride.	Continuous infusion via filter. 0.7-2 units/kg/hr. Titrate dose based on observed circuit lifespan.	Dilute one vial (750u) in 50ml 0.9% sodium chloride. Final concentration 15u/ml. Use 750u/50ml in a syringe. The syringe should be discarded after 24 hours if there is still drug remaining.	Monitor Anti Xa levels, targeting 0.1-0.4 (a higher target may be set if patient is systemically anticoagulated). Monitor platelet count (small risk of cross reactivity in HIT patients).
Argatroban <i>Direct thrombin inhibitor</i> <i>Each vial contains 50mg/50ml</i>	2000ml 0.9% sodium chloride.	Continuous infusion via filter. 30-60mcg/kg/hr. Titrate dose based on observed circuit lifespan.	Draw up one argatroban 50mg/50ml vial neat. Argatroban solution should NOT be stored in direct sunlight, thus all syringes should be covered using an additional infusion sticker to reduce the amount of light exposure to the solution. The syringe should be discarded after 24 hours if there is still drug remaining.	Monitor APTTr and target <1.5 (a higher target may be set if patient is systemically anticoagulated).

Table 15. Anticoagulation options for patients with positive HIT antibody test, low clinical risk and in whom regional anticoagulation with citrate is contraindicated

Sodium disorders during CRRT

Rapid correction of abnormal sodium concentrations can be harmful to the patient, especially if the abnormality is chronic. Wherever possible delay initiation of CRRT whilst the sodium abnormality is investigated and corrected.

When it is not possible to delay CRRT then RAC should not be used, and CRRT should be performed with either no anticoagulation, heparin or epoprostenolol (refer to section 2 of this guide - page 14). The decision to initiate CRRT in patients with severe hyponatraemia or hypernatraemia should be made at consultant level.

In order to avoid rises of $[Na^+]$ more rapid than 6mmol/L/24hours or falls of $[Na^+]$ more rapid than 8-10mmol/L/24hours the replacement fluid bags and dialysate bags need to have added either sterile water (in cases of hyponatraemia, to reduce the sodium content of the fluids – refer to table 16) or 30% sodium chloride (in cases of hypernatraemia, to raise the sodium content of the fluids – refer to table 16). In addition commence CRRT at the lowest acceptable total effluent dose.

$[Na^+]$ should be measured frequently (via arterial or venous blood gases) and a rise or fall of $[Na^+]$ of $>2\text{mmol/L}/6\text{hours}$ should prompt review of CRRT. Either the total effluent dose will need to be reduced, or the dialysate and replacement fluid bags will require further adjustment, or both.

Volume of water added (ml)	Final volume of fluid bag (ml)	Final $[Na^+]$ (mmol/L) in fluid bag	Final $[HCO_3^-]$ (mmol/L) in fluid bag	Final $[K^+]$ (mmol/L) in PrismaSol	Final $[K^+]$ (mmol/L) in Hemosol B0
0	5000	140	35	4.0	0
150	5150	136	34	3.9	0
250	5250	133	33	3.8	0
350	5350	131	33	3.7	0
500	5500	127	32	3.6	0
750	5750	122	30	3.5	0
1000	6000	117	29	3.3	0
1250	6250	112	28	3.2	0

Table 16. Effect of adding sterile water to a standard 5000ml bag of PrismaSol or Hemosol (in cases of hyponatraemia).

Sodium disorders during CRRT

Volume of NaCl 30% added (ml)	Dose of Na+ (mmol)	Final volume of fluid bag (ml)	Final [Na+] (mmol/L) in fluid bag	Final [HCO ₃ ⁻] (mmol/L) in fluid bag	Final [K+] (mmol/L) in PrismaSol	Final [K+] (mmol/L) in Hemosol
0	0	5000	140	35	4.0	0
5	25	5005	145	35	4.0	0
10	50	5010	150	35	4.0	0
15	75	5015	155	35	4.0	0
20	100	5020	160	35	4.0	0

Table 17. Effect of adding NaCl 30% to a standard 5000ml bag of PrismaSol or Hemosol (in cases of hypernatraemia).

Method to alter electrolyte content of PrismaSol or Hemosol B0

This example refers to adding sterile water to reduce [Na⁺]. In order to raise [Na⁺] use NaCl 30% instead of sterile water.

- At all times maintain principles of aseptic non-touch technique.
- Wash hands. Put on gown and sterile gloves. Clean trolley and create sterile field with dressing pack/sterile towel.
- Prepare equipment and place on trolley. Open outer wrapping of spikes, syringe, sterile jug and 3-way tap.
- Remove outer wrapping of replacement and dialysate fluid bags and break compartments to mix contents together, and place on dressing/sterile towel on trolley.
- Place the sterile water for injection polyfusor on dressing/sterile towel on trolley.
- Break the seal open and transfer the required volume of sterile water for injection from the polyfusor into the sterile jug. Any volume remaining should be discarded.
- Spike the replacement and dialysate bags, and place a 3-way tap on the spike to prevent any leakage.
- Add the sterile water for injection to each of the **replacement and dialysate bags**, using the 50ml syringe. Ensure that 4 bags (2 dialysate and 2 replacement) are made up each time to reduce wastage and increase efficiency.
- Mix contents of bags well by shaking.
- Label the bags with the drug additive label. Specify how much of the sterile water for injection you have added.
- Remove 3-way tap from spike to prevent any leakage, prior to connecting to PrisMax machine.

Equipment required to alter electrolyte content of PrismaSol or Hemosol B0

This example refers to adding sterile water to reduce [Na⁺]. In order to raise [Na⁺] use NaCl 30% instead of sterile water.

- 2 x 5000ml replacement fluid bag (PrismaSol or Hemosol B0, depending on patient's [K⁺])
- 2 x 5000ml dialysate bag (PrismaSol or Hemosol B0, depending on patient's [K⁺])
- 1 x Trolley
- Dressing pack/sterile towel
- 2 x Spike
- 1 x 1L sterile jug
- 500ml sterile water for injection polyfusor, number required will depend on total amount of water to be added
(order from pharmacy during working hours 09:00-17:30 and from the EDC out of hours)
- 3-way tap
- 2 x Bungs
- Alcohol (Cliniwipes) wipes
- 1 x 50ml syringe
- Sterile gloves and gown
- 4x Drug additive label

PrisMax display

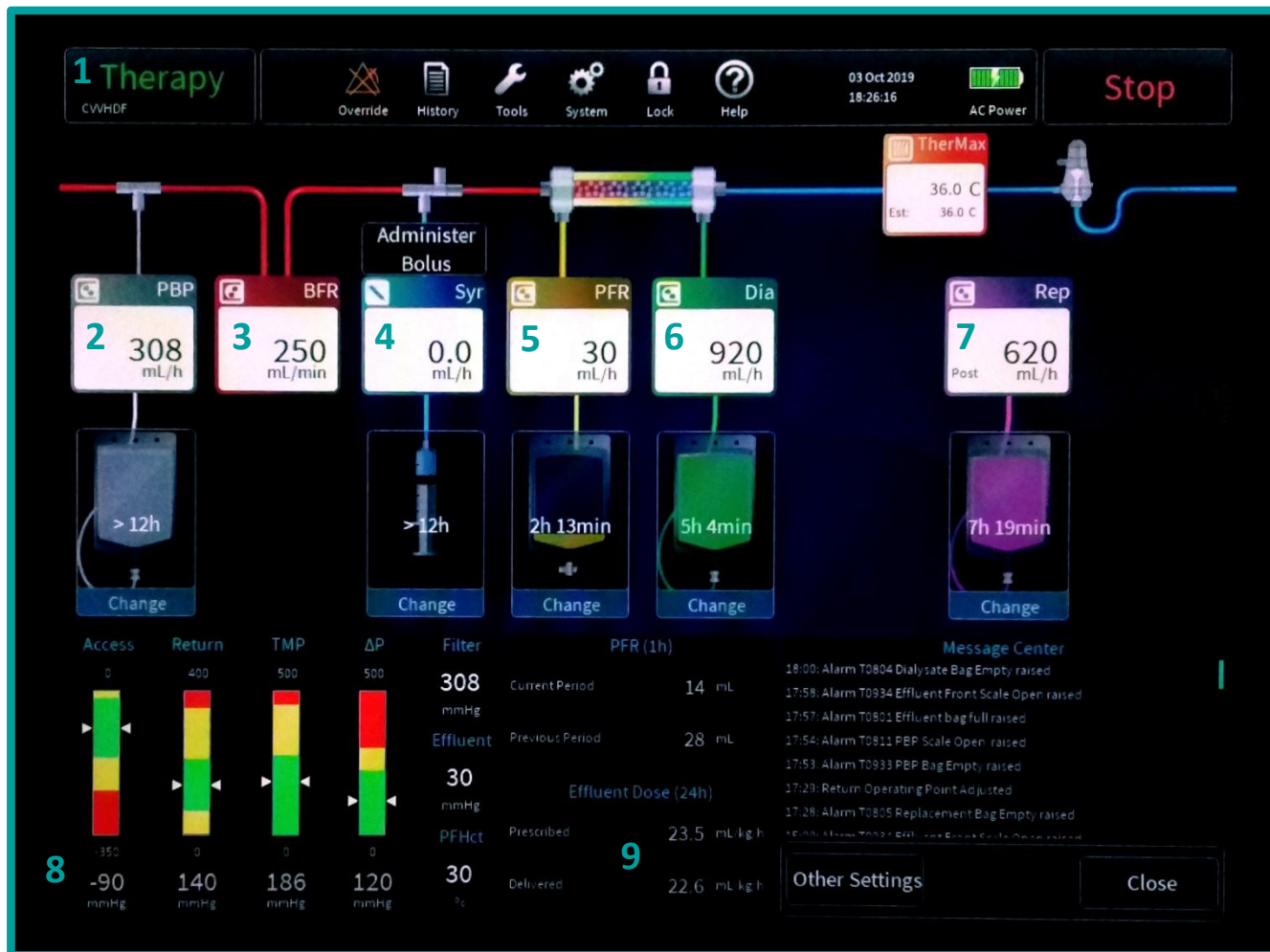


Figure 5. Prismax main display screen

1. Selected therapy
2. Pre-Blood Pump (PBP): Prismictrate when using RAC (otherwise pre-filter replacement fluid)
3. Blood Flow Rate (BFR)
4. Rate of administered anticoagulant (heparin or epoprostenol)
5. Patient Fluid Removal (PFR)
6. Dialysate (Dia): Prismocal when using RAC (otherwise prismaSol or hemosol)
7. Replacement fluid: PrismaSol or Hemosol B0 (whether using RAC or an alternative anticoagulant)
8. Pressure monitoring
9. Total effluent dose