RENAL REPLACEMENT GUIDELINE

CRITICAL CARE AT RIE, WGH AND SJH

NOTE – THIS GUIDELINE NOW INCLUDES ALL ASPECTS OF RRT AND NOT JUST CITRATE INCLUDING:

- RRT IN COVID PATIENTS
- RRT IN ACUTE LIVER FAILURE
- ALTERNATIVE ANTICOAGULATION i.e HEPARIN
- SPECIAL CONDITIONS FOR CONSIDERATION
  - HYPO/HYPERNATRAEMIA
  - HYPERKALAEMIA

Title: Renal Replacement Guideline	
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Status Draft/Final: Final	**Approved by:** Oliver Robinson
	Written:19/06/2018
Reviewed on: 20/09/2021	**Next review :** 23/03/2023

Index **Page number**

Abbreviations:
CVVHD - continuous venovenous haemodialysis
CRRT – continuous renal replacement therapy
Ci-Ca = Citrate-Calcium
ABG = Arterial blood gas
Calcium T : I = Total calcium divided by ionised calcium

QUICK REFERENCE FLOWCHART ON CITRATE ANTICOAGULATION

Step 1 (see page 7)

- **Normalise systemic ionised calcium (Ca) before starting CVVHD**
- **Check Ca on ABG 1 hr before starting and correct as per table 1**
- **Acute liver failure may require different protocol – see page 11**

Step 2 (see page 7)

- **Determine patient's dialysate flow rate use actual body weight**
  - **25ml/kg/hour – see table 2**
  - **35ml/kg/hour in certain circumstances – see table 3**

Step 3 (see page 8)

- **Prescribe the dialysate flow rate, blood flow and fluid removal rate on the 24 hour chart**
- **Prescribe the following 'continuous infusions' within Kardex**
  - **Calcium chloride, Sodium citrate and Ci-Ca dialysate K4/K2 bags – page 8 + picture 1 (page 25) for info/dose**

Step 4 (see page 9)

- **Start citrate at 4mmol/L and check post filter ionised calcium at 5 minutes. Adjust as per table 4.**
- **Start calcium chloride at dose recommended in table 1.**
- **Check post filter and systemic ionised calcium every 6 hours unless table 4 and table 5 indicate otherwise**

Step 5 (see page 10)

- **Record information on ICU CVVHD monitoring sheet**
- **Check and record Calcium T : I ratio daily**
- **Be alert to unexplained metabolic acidosis and risk of citrate accumulation – see pages 13-14**
- **Patients at risk are acute liver failure and severe lactic acidosis**

Introduction

This protocol should be used for all general critical care patients requiring CRRT in RIE, WGH and SJH.

1. Mode of CRRT

- The new therapy is continuous venovenous haemodialysis (CVVHD) which will replace continuous venovenous haemofiltration (CVVH).
- As a result, there will be differences in the delivery and prescription of CRRT.
- **Note:** CVVHD is a fundamentally different process to CVVH. Pre/post dilution techniques are therefore not applicable in CVVHD.
- According to the renal drug handbook the elimination of drugs in CVVHD and CVVH is similar, therefore the same reduction/adjustment principles should be utilised.
    - If concerns consult renal drug handbook or pharmacist.

2. Mode of anti-coagulation

- Regional Citrate will be the first line anticoagulant for most patients requiring CRRT.
- **Prophylactic LMWH/Mini-hep must still be prescribed unless contra-indicated.**

3. Access for CRRT

- Vascular access site in order of preference
    - **RIJV > FV > LIJV > SCV**
- Catheter type and length
    - Double lumen veno-veno catheters for majority of patients
    - Trialysis lines available from ward 215 for appropriate patients
    - 16cm for RIJV
    - 20cm for LIJV and FV
    - 25cm for FV in tall patients or if issues with previous 20cm FV, available from 215

4. Indications for CRRT

- Decision to start CRRT made by the Consultant
- **Clinical Indications:**
    - Potassium > 6.5mmol/L (refractory to medical management)
    - Severe metabolic acidosis (pH < 7.15)
    - Urea >27mmol/L
    - Fulminant liver failure – see later in guideline
    - Uraemic complications: pericarditis, encephalopathy, uraemic bleeding
    - Refractory electrolyte abnormalities: hypo/hypernatraemia, hypercalcaemia
    - Severe poisoning or drug overdose i.e methanol, ethylene glycol or as directed by toxbase
    - Refractory volume overload
    - AKI with multiple organ failure
    - Tumour lysis syndrome with hyperuricaemia and hyperphosphataemia

Citrate summary

- Citrate has two roles:
    1. Regional anticoagulation of the circuit
    2. Acid base balance

1. Regional anticoagulation of the circuit

- Regional citrate anticoagulation works by the binding of citrate to ionised (free) calcium, thereby forming citrate-calcium complexes within the dialysis circuit.
- As a result, the low level of ionised calcium within the circuit prevents clotting by deactivating the clotting cascade.
- During CVVHD, 50% of the citrate-calcium complexes are dialysed out as waste and the remaining 50% return to the patient.
- The following two processes help to aid normalisation of systemic ionised calcium levels:
    - A continuous infusion of calcium chloride into the return line of the circuit.
    - Metabolism of the citrate-calcium complexes by the patient (this releases some of the previously bound ionised calcium).
- The normalisation of the ionised calcium restores the clotting cascade within the patient.

2. Acid base balance

- The citrate-calcium complexes that return to the patient are metabolised by the liver and skeletal muscle to bicarbonate and the free ionised calcium is released.
- In view of this generation of bicarbonate, the dialysate bags have a lower level of bicarbonate than was the case in CVVH.
- However, if the patient is unable to metabolise the citrate-calcium complex, a metabolic acidosis develops due to two factors:
    - Reduced generation of bicarbonate
    - Citrate accumulation (citrate is an acid until it is metabolised to bicarbonate)

Benefits of regional citrate anticoagulation

- Only the circuit is anticoagulated by the citrate
- It can be utilised when systemic anticoagulation is contraindicated
- Lower blood flow required – therefore better tolerated in unstable patients
- Longer circuit life
- Reduced nursing work load

Citrate Protocol

- Regional citrate will be the first line anticoagulant for all patients requiring CRRT.
- 3% of patients develop metabolic acidosis consistent with citrate accumulation[1].
- The following patient groups are examples of those at increased risk of citrate accumulation and **may not** tolerate citrate.
    - **Severe lactic acidosis** (Citrate can be used first line but very careful attention must be paid to the risk of citrate accumulation)
    - **Acute liver failure** (Citrate unlikely to be first line see page 11 where a different protocol maybe required)
- For patients suspected of developing **citrate accumulation** (toxicity) see pages 13-14 for management.
- **Prophylactic LMWH/Mini-hep should still always be prescribed unless contra-indicated as citrate only anticoagulates the filter circuit**

Citrate Accumulation (Toxicity) vs Excessive Citrate Metabolism

- The above 2 terms are often **incorrectly** used inter-changeably.
- These are **two completely separate conditions** that must be identified and require different treatments in a timely manner to prevent harm
- Further information is provided later in the protocol regarding these separate conditions however a simple explanation of the two is:

1. **Citrate Accumulation (toxicity)** – the more serious of the two refers to the accumulation of **unmetabolised** citrate within the body resulting in potentially life threatening **metabolic acidosis** (citrate is an acid until it is metabolised to bicarbonate)**.** Patients at risk include those with:
    a. Severe lactic acidosis
    b. Acute liver failure

2. **Excessive Citrate Metabolism –** refers to the excessive generation of bicarbonate due to excessive metabolism of citrate resulting in a metabolic alkalosis. The cause of this is often multi-factorial but is most commonly due to the filter membrane becoming less efficient and therefore more citrate-calcium complexes are returned to the patient and metabolised to bicarbonate. See page 15 for more details.

How to perform citrate anticoagulation

Step 1 – Management of patient's systemic ionised calcium pre-CVVHD

- It is important to check and normalise systemic ionised calcium prior to commencing CVVHD. Approximately 1 hour prior to commencing CVVHD, perform an ABG.

- If systemic ionised calcium < 1.12 give a pre-treatment bolus of either:
  - **10mmols calcium chloride (10mls) in 50mls Nacl 0.9% over 30 mins CENTRALLY**
  - **30mls of calcium gluconate 10% over 30 mins (if calcium chloride not available)**

- Then select the starting prescription of calcium chloride from **Table 1**.
  (Note: you do not need to repeat an ABG following the bolus dose of calcium)

Table 1

Systemic ionised Calcium (mmol/L) (Arterial Line)	**<1.01**	**1.01 – 1.11**	**1.12 – 1.20**	**1.21 – 1.45**	**>1.45**
Calcium pre-treatment bolus required?	**Yes**	**Yes**	No	No	No
Starting prescription of calcium chloride (mmol/L of filtrate)	2.2	2.0	1.9	1.5	1.4

Step 2 – Dialysate flow rate

- **The default dialysate flow rate is 25ml/kg/hour (Table 2). Use actual body weight.**

Table 2 – Based on approx. 25ml/kg/hour – Actual body weight

Weight	**<60kg**	**60-69kg**	**70-79kg**	**80-89kg**	**>90kg**
Dialysate flow rate (ml/hr)	1400	1600	1800	2000	2200
Blood flow rate (ml/min)*	70	80	90	100	110
Citrate dose (mmol/L)	4.0	4.0	4.0	4.0	4.0
Fluid removal rate (ml/hr)	CLINICIAN DECISION ON INDIVIDUAL PATIENT BASIS				

- Consider increasing dialysate flow rate to **35ml/kg/hour (Table 3)** in the following:
  - Severe metabolic acidosis: pH < 7.1 (see page 12 for more on metabolic acidosis)
    - **Note if the metabolic acidosis is due to citrate accumulation increasing to 35mls/kg/hour may worsen the acidosis**
  - Severe hyperkalaemia (K+ > 6.5)
  - Inadequate response to 25mls/kg/hour
  - Poisoning (e.g. ethylene glycol)
  - Rhabdomyolysis

Table 3 – Based on approx. 35ml/kg/hour – Actual body weight

Weight	**<60kg**	**60-69kg**	**70-79kg**	**80-89kg**	**>90kg**
Dialysate flow rate (ml/hr)	1800	2200	2600	2800	3000
Blood flow rate (ml/min)*	90	110	130	140	150
Citrate dose (mmol/L)	4.0	4.0	4.0	4.0	4.0
Fluid removal rate (ml/hr)	CLINICIAN DECISION ON INDIVIDUAL PATIENT BASIS				

*During citrate anti-coagulation the ratio of dialysate flow rate to blood flow rate **should not be changed**. It should always be 20:1 (dialysate flow rate [ml/hr] : blood flow rate [ml/min]). Note the different units. Any change in this ratio will affect citrate delivery or excretion and therefore affect acid-base balance. However in non citrate (i.e heparin) dialysis the ratios will change as the blood flow rate will need to be increased to prevent clotting within the circuit.

Step 3 – Prescription

- Prescribe on the 24-hour chart:
  - Dialysate flow rate (ml/hr) based on patient weight - **see Table 2 or 3**
  - Fluid removal rate (ml/hr). (This is a clinical decision on an individual patient basis and is **different** from the blood flow rate in tables 2/3)

- Sign the following in the haemofiltration section of the 24-hour chart (see picture 1):
  - Calcium chloride 150mmols in 1500mls (100mmols/L)
  - Sodium citrate 4% 1500mls
  - Ci-Ca dialysate K4 (Potassium 4 mmol/L)
  - Ci-Ca dialysate K2 (Potassium 2 mmol/L)
    - **This should only be used for patients with an elevated potassium level >6.5mmol/L.** Once the potassium reaches **5mmol/L** change back to Ci-Ca dialysate K4 bags.
      - If Ci-Ca dialysate K2 bags are not available and the K+ is >6.5mmol/L, an alternative strategy would be to filter the patient at 35mls/kg/hour until the potassium returns to safe range. Following this the dialysate rate could be reduced back to the standard 25mls/kg/hour dose if deemed appropriate.
      - In addition medical management of potassium can also be used while the patient is filtered until the potassium returns to a safe range.

Step 4 – Treatment and Monitoring

A) Citrate dose

- Set initial citrate dose to **4mmol/L** of blood.
- **5 minutes** after commencement of therapy check a post filter ionised calcium (**venous/blue sampling port**) to ensure circuit anticoagulated (adjust as per **Table 4**).
- Then check 6 hourly from venous/blue sample port.
- **More frequent checks than 6 hourly should not be done** as this will mean changes made earlier to citrate dose will not have had time to take effect.

Table 4 – Citrate dose adjustment

Post filter ionised calcium (mmol/L) (venous/blue port)	Change of citrate dose (per litre of blood)	Check post-filter ionised calcium and review citrate dose after
> 0.40	Increase by 0.2 mmol/L and inform medical staff	6 hours
0.35 – 0.40	Increase by 0.1 mmol/L	6 hours
0.25 – 0.34	No change	6 hours
0.20 – 0.24	Decrease by 0.1 mmol/L	6 hours
< 0.20 or ** or ↓↓↓↓**	Decrease by 0.2 mmol/L	6 hours

B) Calcium dose

- See table 1 for initial dose and whether pre-treatment required.
- See table 7 for liver patients with lactate > 8 mmol/L and Calcium T:I ratio > 2.
- Systemic ionised calcium level should be taken from the patient's **Arterial Line**.
- An immediate systemic ionised calcium is not required (unlike post filter calcium).
- First check at 6 hours and then as directed by **Table 5**.
    - There is often an initial fall in calcium as the patient goes onto CVVHD. Time is required for equilibration to occur hence wait for 6 hours before first check.
- In patients where there has been a significant fall in systemic ionised calcium more frequent checks may be required.

Table 5 – Calcium chloride dose adjustment

Systemic ionised calcium (mmol/L) (arterial line)	Change of calcium dose (per litre of filtrate)	Check systemic ionised calcium and review dose after
> 1.35	Decrease by 0.4 mmol/L and inform medical staff	6 hours
1.21 – 1.35	Decrease by 0.2 mmol/L	6 hours
1.12 – 1.20	No change	6 hours
1.00 – 1.11	Increase by 0.2 mmol/L	6 hours
< 1.00	Increase by 0.4 mmol/L inform medical staff	**2 hours**

Step 5 - Documentation and Monitoring

- **Use 24 hour chat to document results (previously we used a monitoring chart this is no longer required)**
- Record post filter and systemic ionised calcium results as directed by tables 4/5.
    - **Note in cases of low systemic ionised calcium more frequent checks are required** (see table 5)
- Calculate and record calcium T : I ratio daily

Calcium T : I Ratio

- Calculate the ratio of total calcium to systemic ionised calcium **DAILY**
    - Obtain total calcium from laboratory bloods.
      (Note: ***Do not*** correct for albumin)
    - Obtain systemic ionised calcium from most recent ABG.
    - Calcium T:I Ratio = total calcium divided by systemic ionised calcium.
- Calcium T:I ratio > 2.5 indicates citrate accumulation see page 13.

Circuit life

- The circuit should run for a maximum of 72 hours after which a change in circuit is required.
- In the future we may extend the circuit life – as we gain more experience with citrate.

Acute liver failure patients

- See also specific ICU protocol **"Fulminant Liver Failure**" on intranet for further information regarding the importance of CVVHD

- **Acute liver failure patients are at very high risk of cerebral oedema therefore:**
    - **Ventilated patients with > 2 of the following risk factors require immediate RRT (even if patient has acceptable renal function/urine output):**
        - Age < 40 (most important risk factor)
        - Hyperacute presentation (i.e. paracetamol overdose or drug induced)
        - Ammonia > 150
        - High level of vasopressor support
        - Renal dysfunction/significant metabolic acidosis

- **Dosing of RRT**
    - When commencing RRT in acute liver failure always use high (maximum) volume exchanges no matter the indication
        i. No anti-coagulation in first instance including no citrate (see page 17 on how to perform with no anticoagulation)
        ii. Aim for maximum dose of renal replacement by setting flows to:
            1. **Blood flow 250 - 350mls/min (if tolerated)**
            2. **Dialysate flow to 4.8Litres/hour**
        iii. **Commence 5% hypertonic saline infusion initially at 50mls/hour to try and maintain therapeutic hypernatraemia of > 145mmol/L. (Boluses of 5% hypertonic saline 125mls can still be given in-addition for raised ICP, pupillary changes and hyponatraemia)**
        iv. Consider fluid removal if tolerated to ensure patient not becoming overloaded

- If the filter clots off and the acute liver failure is deemed to be recovering or the patient receives a transplant the patient can be commenced on citrate. **The circuit blood and dialysate flows will however need to be reduced back to recommended citrate levels**

- Patients with acute liver failure who are commenced on citrate are likely to have increased calcium requirements.

- Check lactate and calculate Calcium T:I ratio (see page 10 for calculation) in all acute liver failure patients who are to be commenced on CVVHD with citrate anticoagulation.

- Review these patients on a regular basis with senior medical staff and observe for signs of citrate accumulation (see pages 13-14 for management), **more than one of:**
    - **Marked drop in systemic ionised calcium**
    - **Unexplained metabolic acidosis**
    - **Calcium T:I ratio > 2.5**
    - **Elevated total calcium > 3mmol/L**

Renal Replacement therapy in COVID +ve or suspected patients

COVID-19 patients may present the following challenges when considering RRT :

1. Septic/HLH/Cytokine storm and are therefore likely to require higher dose RRT in the form of 35mls/kg rather than 25mls/kg
2. Pro-thrombotic and therefore may require additional anticoagulation while on RRT

Setting the RRT dose in COVID +ve patients

- **If using citrate anticoagulation**
    - You may wish to choose a higher dose of RRT than normal (as above)
    - Consider the 35mlg/kg table in the citrate/RRT guideline
    - You may wish to move up the weight categories to further increase the dose of RRT delivered
    - Maximum settings for citrate are blood flow 180mls/min and dialysate flow 3600mls/hour
    - As always, monitor for citrate toxicity

- **If using multibic/heparin**
    - This can deliver a higher dose of RRT compared to citrate which maybe useful in patients with cytokine storm
    - Maximum settings are blood flow 250-450mls/min and dialysate flow of 4800mls/hour

Anticoagulation while on RRT in COVID +ve or COVID suspected patient

- **Step 1:** Determine if any indications for starting systemic IV heparin i.e. suspicion of PE. Have a very low threshold for starting systemic IV heparin in COVID +ve requiring RRT. Furthermore check whether patient in anticoagulation arm of REMAP-CAP study – crossover in this study is allowed but this information may help inform your decisions regarding anti-coagulation.
- **Step 2:** If no indications for IV heparin start on CVVHD using citrate anticoagulation and continue enchanced prophylactic dalteparin, see COVID critical care VTE protocol while monitoring anti Xa levels
- **Step 3:** If clots once on citrate – start treatment dose systemic IV heparin (1000units/ml) as per Critical Care adult heparin infusion chart for COVID-19 positive patients. Aiming for unfractionated heparin level of 0.3-0.7. This guideline/chart is a separate document and is either found in the specific RRT in COVID guideline in the COVID section of the intranet, or in the COVID section of the intranet under anti-coagulation section entitled “heparin infusion chart in COVID-19”. Note the Critical Care COVID-19 IV heparin infusion is weight based which is different from the standard NHS Lothian policy (5000units loading and then 1200units/hour) as COVID patients require more heparin. **Also do not use the standard heparin dosing for RRT circuit anti-coagulation as this is a different concentration of heparin (250units/ml) with a different target APTT(r).**
- **Step 4:** Note IV heparin can be given in addition to citrate anticoagulation or alone with multibic. Determine which is best and consider stock levels before deciding:
    - **Switch to IV heparin and multibic?**
        - Can give better clearance as maximum dialysate flow rate higher

- **Continue citrate with IV heparin?**
  - Continuing citrate in addition to IV heparin may prevent clotting and prolong filter life
- Titrate IV heparin using **unfractionated heparin assay (search heparin on trak)**. Note APTT ratio can be inaccurate in COVID-19 hence we now use unfractionated heparin assay in these patients.

Action plan if running out of CVVHD machines due to excess demand in COVID Pandemic

- There are concerns that there may not be enough CVVHD machines for the number of patients who require them
- **Continue to use CVVHD as normal until demand exceeds the number of available machines**
- Subsequently follow this protocol

1. **UNSTABLE PATIENTS** (Those with hyperkalaemia, life threatening diuretic resistant fluid overload or severe acidaemia)
   - Should receive CVVHD as per normal protocol with a filter change every 72 hours or longer.

2. **STABLE PATIENTS (when not enough CVVHD machines available)**
   - Depending on resources and patient stability they can either receive
     i. **High dose CVVHD delivered over 12 to 24 hours**
        - This will allow CVVHD machines to be used between different patients however will have a significant impact on consumables.
        - Multibic/heparin **will give better clearance as dialysate flow rate higher**
        - **Beware** – when using citrate for high dose CVVHD patients there is an increased risk of citrate toxicity as higher blood flows than normal are utilised therefore more citrate delivered to patient

     ii. **Intermittent haemodialysis (IHD)**
        - Try high dose CVVHD delivered over 12 to 24 hours in the first instance
        - Renal are able to provide IHD but will need prior notice preferably > 24 hours (PTO)
        - IHD can be provided in cubicles 16 and 17 in 118, 117 and 116D as these spaces have the correct water supply – move patient to these areas where possible
        - Remaining 118/116 beds v.difficult to provide IHD as will require a v.bulky reverse osmosis machine from renal

- **Multibic/heparin vs citrate for High dose CVVHD**
    - Option 1 ***Preferred*** **multibic/heparin** (will give better clearance as dialysate flow rate higher)
    - Option 2 **citrate** (useful if v stable, just for ultrafiltration, no issues e.g. liver) ***Need to consider stock levels when deciding between treatment options***

i. Multibic/heparin settings for High dose CVVHD

a. Decide regarding anticoagulation – systemic IV heparin aiming full anticoagulation. Other anticoagulation available.
b. Blood flow 250-450mls/minute (initially as tolerated)
c. Dialysate flow to 4800mls/hour initially
d. Fluid off to 250-450mls/hour (as directed by required fluid balance)

ii. **Citrate settings for High dose CVVHD**

a. Blood flow to 180mls/min initially
b. Dialysate flow to 3600mls/hour initially
c. Fluid off to 250-450mls/hour (as directed by required fluid balance)
d. Note patients at slightly higher risk of citrate toxicity and hypocalcaemia

Metabolic acidosis

- If the patient is unable to metabolise citrate a metabolic acidosis develops due to:
    - Citrate accumulation (toxicity) as citrate is an acid until metabolised
    - Reduced generation of bicarbonate

- Any patient is at risk but specifically patients with:
    - **Acute liver failure**
    - **Severe lactic acidosis**

If a metabolic acidosis fails to improve or develops de-novo it is important to distinguish if it is due to a primary metabolic process or due to the accumulation of citrate.

Potential causes of metabolic acidosis and actions include:

- Patients underlying condition:
    - Treat as appropriate
- CVVHD has not been running long enough:
    - Recheck acid base in due course
- Inadequate dialysis dose:
    - Trial of increasing dialysis flow rate to 35mls/kg/hr
    - **Note if the metabolic acidosis is due to citrate accumulation this increase may worsen the acidosis**
- Citrate accumulation (toxicity) due to impaired metabolism
    - See pages 13-14

Citrate accumulation (toxicity)

Citrate accumulation (toxicity) - refers to the accumulation of **unmetabolised** citrate within the body resulting in potentially life threatening **metabolic acidosis** (citrate is an acid until it is metabolised to bicarbonate)**.**

Signs that citrate accumulation (toxicity) is developing include (more than one of):

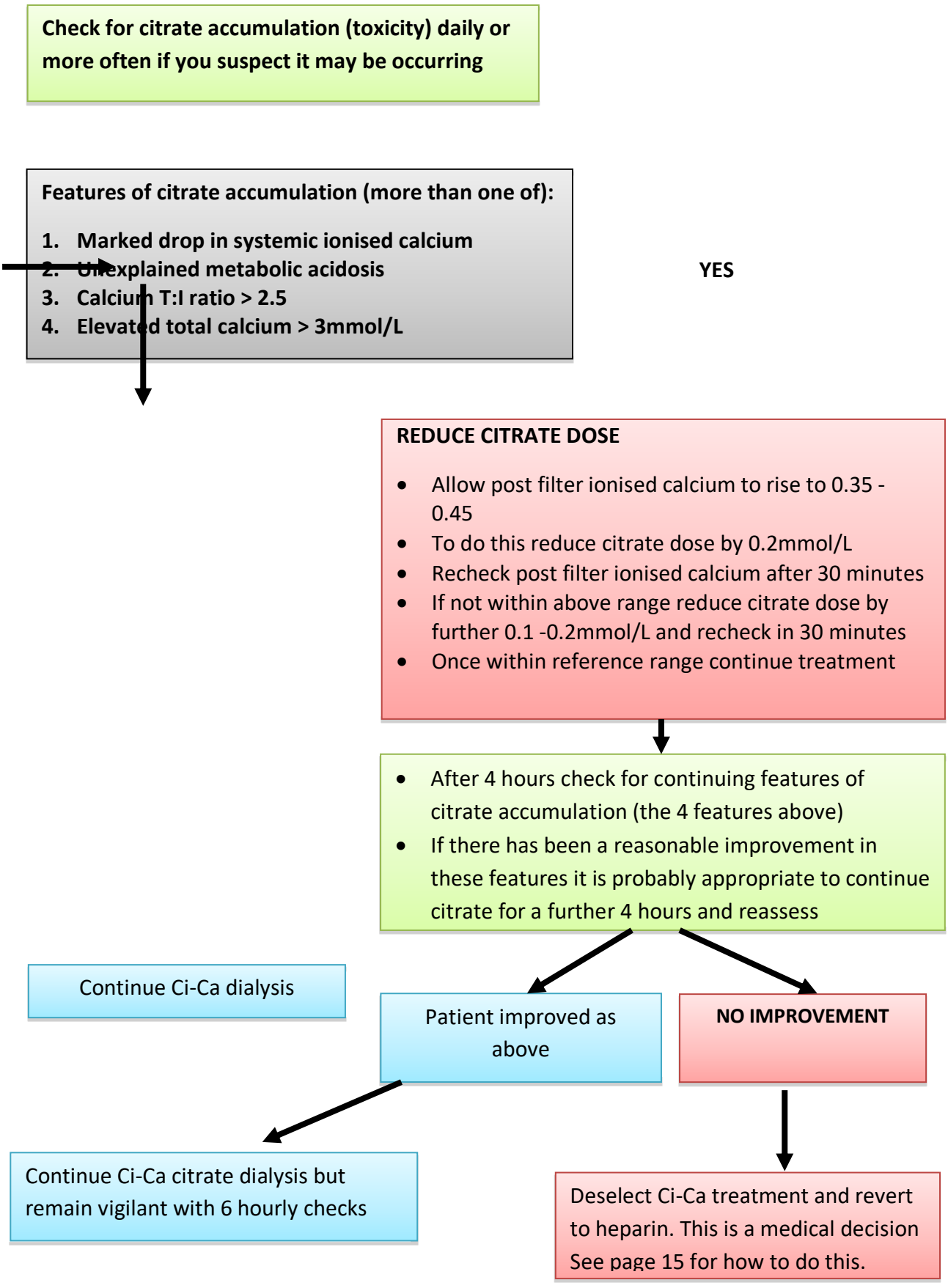
1. **Marked drop in systemic ionised calcium (increasing need for calcium replacement)**
2. **Unexplained metabolic acidosis**
3. **Calcium T:I ratio > 2.5**
4. **Elevated total calcium > 3mmol/L (do not correct for albumin)**

- The Fresenius machine will prompt consideration of citrate accumulation if the infusion dose of calcium chloride is > 2.1mmol/L.
- **See citrate accumulation flow chart on page 14.**

Why does a Calcium T:I ratio > 2.5 indicate citrate accumulation (toxicity)?

- A drop in the systemic ionised calcium will occur if the citrate-calcium complexes are not being metabolised and therefore bound calcium is not released as ionised calcium.
- Additional calcium chloride replacement will therefore be required as directed by table 5
- However total calcium increases as all forms of calcium including the calcium that is still bound to citrate are measured by the laboratory analyser.
- This results in a change in the ratio of total body calcium to ionised calcium.
- In summary rising total calcium and falling ionised calcium indicates citrate accumulation and results in a raised T : I ratio

Management of Citrate Accumulation (Toxicity) Flow Chart - (Figure 1)



Metabolic Alkalosis while on CVVHD

Check patients bicarbonate and base excess daily while on CVVHD. A base excess of +3 or a bicarbonate > 33 requires a review and action to be taken.

- **Causes**
  - **Excessive citrate metabolism** is most common
  - Medication causing alkalosis
  - Patient's underlying condition
  - Unknown patient factors

Excessive Citrate Metabolism

- This is down to the filter membrane becoming less efficient and clogging up – therefore less citrate dialysed out in waste product and more citrate is infused into the patient.
- This additional systemic citrate is metabolised to bicarbonate therefore creating the alkalosis.
- This is not citrate accumulation (toxicity) as that would produce a metabolic acidosis this is just excessive citrate metabolism.
- Signs of filter becoming less efficient/clogging include:
  - Rising bicarbonate
  - Increasing systemic calcium
  - Reduced need for calcium infusion on CVVHD
  - Poor clearance of urea and creatinine
  - Increasing sodium

- **Management**
  - **A base excess of +3 or a bicarbonate > 33 should trigger a review**
  - Review medications
  - Change the filter (as it maybe clogging)
  - If the patient has good clearance it maybe appropriate to dialyse less aggressively for a 90kg patient choose a dose of 25mls/kg but instead set the patients weight as <60kg – see table 2
  - Changes to the blood flow rate or dialysate flow rate to decrease citrate delivery or increase citrate removal can be performed. Note the following changes will mean that the dialysate flow rate to blood flow rate will no longer be 20:1. In **exceptional circumstances** this is allowed and this is one of these circumstances.
    - First decrease blood flow by 20ml/min (but do not reduce below 80mls/min). This will mean less citrate delivered to the patient.
    - Improvement in alkalosis is likely to be slow therefore allow 6 hours and then check blood gas to see if there has been an improvement in metabolic alkalosis
    - If not increase dialysate flow by 500mls/hour. This will mean more citrate dialysed out.
  - If the above steps fail to resolve the metabolic alkalosis it maybe appropriate to stop citrate and use alternative anticoagulation for the filter

Alternative anticoagulation

1. CVVHD with heparin or epoprostenol or argatroban

A change to alternative anticoagulation can be made in the following circumstances:

- If citrate accumulation (toxicity) does not respond to corrective measures
- Consultant request
- Failure of citrate to adequately anticoagulate the circuit
- Patient requires systemic IV heparin for another indication
    - **In the majority of cases citrate should still be used in addition to heparin** as it is just regional anticoagulation and there is no contraindication to running both heparin and citrate at the same time.

To start heparin or epoprostenol or argatroban:

- The heparin or epoprostenol protocol/doses used is the same as was previously used for the Baxter aquarius machines.
- Argatroban – commonly used in HIT. Discuss with haematology and refer to haematology guideline (it is titrated to APTT)
- To determine epoprostenol protocol refer to critical care drugs A-Z -> epoprostenol
    1. Note epoprostenol must be given via a dedicated central line port and **NOT through the frensenius machine**
- To determine heparin dose refer to the previous critical care CVVH heparin anticoagulation guideline on the critical care intranet under renal and urology -> RRT
- Heparin can be given via the Fresenius machine or via a separate infusion pump
    1. Note sometimes the Fresenius machine does not recognise different 50mls syringes – hence a separate infusion pump may be required
- Deselect citrate (Ci-Ca) from the menus tab when ready to start heparin
- **You must follow steps 1-3:**
    1. **Change the dialysate bags to Multibic 4**
        - **You must not** use the Ci-Ca dialysate bags as this will cause a **life threatening hypocalcaemia.**
        - **Multibic 0 is no longer used as CVVHD is different from CVVH.** Therefore we should never dialyse against a potassium concentration of 0.
        - When using non citrate therapy the only option is to dialyse against a potassium of 4mmol/l (Multibic 4). Therefore if the potassium is very high use medical management in addition to CVVHD until the potassium has returned to acceptable limits.
    2. **Increase the blood flow rate to a minimum of 250mls/min**
        - The dialysate flow rate to blood flow rate **no longer** needs to be maintained at 20:1 like in citrate dialysis as per tables 2/3. The 20:1 ratio was required in citrate for acid base control, however as citrate has been deselected this ratio is no longer required. The blood flow increase is required to prevent the circuit clotting. Previously pre-dilution was used to help with this but as the switch has been made to CVVHD this is not possible.

- Due to the lack of pre-dilution you may find that higher doses of heparin are required compared to the previous CVVH modality.

3. **Increase dialysate flow to a minimum of 2600mls/hour**
   - The increase in dialysate flow is required to maintain the efficiency and clearance of the filter.
   - If extra clearance is required you can increase the dialysate flow rate to a maximum of 4800mls/hour.

2. CVVHD with no anticoagulation

- This maybe appropriate in patients with severe coagulopathy
- Read page before on CVVHD with heparin as the same important principles and rationale apply on how to perform
- **AS PAGE BEFORE again follow steps 1-3:**
  1. **Change the dialysate bags to Multibic 4**
     - **You must not** use the Ci-Ca dialysate bags as this will cause a **life threatening hypocalcaemia.**
     - **Multibic 0 is no longer used as CVVHD is different from CVVH.** Therefore we should never dialyse against a potassium concentration of 0.
     - When using non citrate therapy the only option is to dialyse against a potassium of 4mmol/l (multibic 4). Therefore if the potassium is very high use medical management in addition to CVVHD until the potassium has returned to acceptable limits.
  2. **Increase the blood flow rate to a minimum of 250mls/min**
     - The dialysate flow rate to blood flow rate **no longer** needs to be maintained at 20:1 like in citrate dialysis as per tables 2/3. The 20:1 ratio was required in citrate for acid base control, however as citrate has been deselected this ratio is no longer required. The blood flow increase is required to prevent the circuit clotting. Previously pre-dilution was used to help with this but as the switch has been made to CVVHD this is not possible.
     - Due to the lack of pre-dilution you may find that higher doses of heparin are required compared to the previous CVVH modality.
  3. **Increase dialysate flow to a minimum of 2600mls/hour**
     - The increase in dialysate flow is required to maintain the efficiency and clearance of the filter.
     - If extra clearance is required you can increase the dialysate flow rate to a maximum of 4800mls/hour.

Special Conditions for consideration

Hyponatraemia (Na < 125mmol/L) – prior to starting CVVHD

- Rapid correction of hyponatraemia of more than 48 hours duration is not recommended
- Hyponatraemia should not be corrected by **>8-10mmols**/day due to the real risk of **central pontine demylination**
- CVVHD may result in rapid correction of sodium in hyponatraemic patients due to 2 mechanisms:
    1. Citrate is presented as sodium citrate 4% this contains 408mmol/L of sodium. Therefore hyponatraemic patients on citrate therapy may experience a more rapid correction in sodium than desired.
    2. When not using citrate the Multibic filter bags contain 140mmols/L of Sodium. As the patient is dialysed against these bags there may be a more rapid correction in sodium than desired.

- **Management – ways to prevent rapid correction of sodium in hyponatraemic patients requiring CVVHD:**
    1. When choosing to filter a hyponatraemic patient choose a much lower dose of dialysis than you would normally i.e for a 90kg patient choose a dose of 25mls/kg but instead set the patients weight as <60kg – see table 2.
    2. Monitor the patient's sodium hourly and if the rate of rise of sodium is too rapid you may need to temporarily stop the filter for several hours to prevent complications.
    3. Infuse 5% dextrose at a set rate while the patient is on the filter to try and prevent rapid correction of sodium.

Hypernatraemia – maintaining therapeutic Hypernatraemia while on CVVHD

- Patients with the following conditions may require targeted therapeutic hypernatremia 145-150mmol/L while on CVVHD.
    1. Fulminant liver failure with concerns regarding cerebral oedema
    2. Traumatic brain injury patients at risk of raised ICP
- It can be difficult to maintain sodium at the desired level as the patient is being continuously filtered against a fixed concentration of sodium in the dialysate bag

- **Management**
    1. Commence continuous infusion of 5% hypertonic saline to maintain sodium within the desired range
    2. Commence infusion rate at 50mls/hour increasing as required up 100mls/hour

Hyperkalaemia

- Patients potassium **>6.5mmol/L**
    - If on citrate dialysis
        - Switch to CiCa K2mmol/L bags (from K4mmol/L)
        - Increase dialysis flow rate to 35mls/kg/hour as per table 3

- If still no effect increase to the maximum flows allowed on citrate ignoring the patients actual weight and set the flows to 150mls blood flow and 3000mls dialysate flow. Monitor carefully for citrate toxicity.
- If hyperkalaemia remains refractory:
    1. Ensure the circuit is fresh and changed at least 24 hourly as it may become clogged, particularly in cases of rhabdomyolysis
    2. Continue to treat medically if required with insulin/dextrose and IV bicarbonate (if acidotic)
    3. Next depending on situation try either:
        a) Stopping citrate and change to multibic with maximum flows 250-350mls blood flow and dialysate flow of 4.8L. However note NHS Lothian only stocks multibic K4mmol/L unlike citrate which comes in K2mmol/L and K4mmol/L. However with the increased flow this may be enough to bring the potassium down
        b) Add in a second filter on maximum settings. However never have both filters running citrate as this is highly likely to cause toxicity. So ensure one multibic and citrate filter or both multibic filters on maximum settings as above.
    4. If failing to gain control with 2 filters it is likely the patient has massive cellular necrosis incompatible with life

- If patient initially on heparin /other/nothing
    - Keep patient on Multibic K4 (no other concentration of potassium dialysis fluid will be available)
    - Ensure blood flow at least 250mls -350mls/minute
    - Ensure dialysate flow at minimum 2600mls/hour. If already at 2600mls/hour increase up to the maximum rate of 4800mls/hour
    - Treat medically in addition if required with insulin/dextrose and IV bicarbonate (if acidotic)
    - Follow steps in paragraph above for adding in second filter

<u>High volume exchange in patients not on citrate therapy</u>

- In patients requiring high volume exchanges who are not on citrate such as patients with fulminant hepatic failure the following settings should be used:
    - Blood flow 350mls/min (if tolerated)
    - Dialysate flow 4.8Litres/hour (this is the maximum allowed on the Fresenius machine)

Frequently asked questions/Trouble shooting

Note the trouble shooting guide is integrated into the Fresenius MultiFiltrate Pro and therefore there is not a paper version.

Premature filter failure/clotting of filter on citrate anticoagulation

1. Check Vascath
    - Easy aspiration/flush? Is it kinking with patient movement?
    - Anticoagulation **CANNOT** compensate for poor vascular access
    - Consider replacing vascath
    - Beware just reversing the lines makes the vascath much less efficient by causing recirculation – it may be better to insert a new vascath
2. Consider pro-coagulant illness
    - **HIT (this is one of the most common reasons for filter clotting)**
    - DIC
    - Antithrombin III deficiency
    - Hyperlipidaemia or propofol infusion syndrome
    - **Discuss with haematology if concerned** - further urgent investigations maybe warranted
3. Increase flow rates
    - Consider increasing blood flow rates. Note the blood flow to dialysate flow rate must remain at a ratio of 20:1. See table 3 this has higher blood flows as the dialysate rate is set at 35mls/kg/hour.
4. Ensure target post filter calcium results within specified range of 0.25-0.34
    - Consider reducing target filter post filter calcium to 0.2 – 0.24 by increasing citrate rate (if not suitable for IV heparin in addition to citrate)
5. Start IV heparin (if no contraindications) or other anticoagulation in addition to regional citrate anticoagulation

What happens if you use the wrong dialysis solution during citrate (Ci-Ca) therapy?

- If you use Multibic during Ci-Ca therapy you may encounter
    - Systemic bicarbonate increasing
    - Systemic ionised calcium increasing
    - Post filter ionised calcium high with citrate requirements increasing

Low Pressure Return Alarm on filter

- Currently within NHS Lothian we have kept our original Vascath lines and have not changed to the Fresenius shotgun catheters for a variety of reasons.
- As the new Fresenius filter machines use lower blood flow than previous filters and the current vascaths are a wider diameter than the Fresenius shotgun catheters this can occasionally result in the machine detecting low pressure on the RETURN limb of the circuit.
- This alarm may occasionally repeatedly stop the blood flow within the circuit and increase the risk of circuit loss.

- **Possible solutions to this problem are:**
    - Lying the patient flat to increase venous pressure within the patient therefore cancelling the low pressure return alarm
    - Increasing the blood flow in the circuit (while maintaining the 20:1 ratio). Increased blood flow will generate more pressure in the venous system and will hopefully cancel the low pressure alarm
    - Move the vascath to the femoral region where venous pressure is higher and unlikely to cause a low pressure alarm
    - Giving a fluid bolus

- If you have persistent problems with low pressure alarms please inform **oliver.robinson1@nhs.net** as we may need to change to the shotgun catheters in future.

What if the patient does not have an Arterial Line?

- If no A-line available systemic calcium results can be taken from a peripheral vein
- However, this sample **must not** be taken from a vein that is close to the vascath as you are likely to pick up an incorrect calcium level in the patient
    - i.e you can't take the venous sample from a LIJ central line even though the vascath in the RIJ as they both terminate in the same place

Reversing the filter lines

- This is commonly done by nursing staff when the filter is not running well
- However this leads to increased recirculation and can significantly affect the filters clearance of solute
- It may therefore be appropriate in these circumstances to insert a new vascath rather than reversing the lines

What changes need to be made if a patient is disconnected from the circuit

- Providing there has been no change in the patient's clinical state and it is not more than 4 hours since the circuit was disconnected, patients can be reconnected using the previous dialysate and bloods flows, and citrate and calcium doses.

What methods of temporary disconnection are available?

Method 1 – Wash back and recirculate

The maximum disconnection time with this method is **4 hours**

Requirements: 1 litre bag of sodium chloride 0.9%, three way tap or Y connector and single spike adapter, dressing pack and equipment to flush catheter.

1. Press **STOP**

2. Disconnect the arterial line (RED) and connect to the Y connector or three way tap attached to the sodium chloride 0.9% bag
3. Press **START/RESET** this will restart the blood pump and wash back blood to the patient.
4. The optical detector will detect sodium chloride 0.9% solution. The blood pump will stop. A yellow warning will be displayed informing you that the above change has been detected.
5. Press **START/RESET** the machine will then ask you to confirm if you have interrupted the treatment. Press **YES**. The blood pump will now restart.
6. Decide how much blood you want to be returned to the patient. Press **STOP** when you have reached the amount you wish to be returned.
7. Disconnect the venous line **(blue)** from the patient and connect to the Y connector or three way tap attached to the sodium chloride 0.9% bag.
8. Press **START/RESET** and the machine will then be recirculating. (Balancing will automatically switch off).
9. Turn ultrafiltration/fluid off to 0. **Remember to turn it back on when you reconnect the patient.**

To reconnect the patient

1. Press **STOP**
2. Disconnect the arterial (RED) and venous (BLUE) lines from the sodium chloride 0.9% bag and connect to the patient access as per protocol.
3. Press **START/RESET** and the blood pump will restart.
4. A yellow warning will be displayed when the optical detector has detected blood.
5. Press **START/RESET** this will restart the blood pump (Balancing will automatically switch on)
6. Turn ultrafiltration/fluid off to the desired removal rate.

Method 2 – Re-circulate with whole blood – e.g when transferring bed space

This method can be used for disconnections last **not more than 30 minutes**

Requirements: Blue adapter from kit (or three way tap or Y connector).

1. Press **STOP,** this will stop the blood pump
2. Disconnect the arterial (RED) line and connect it to the adaptor
3. Disconnect the venous (BLUE) line and connect it to the other side of the blue adapter
4. Press **START/RESET** this will restart the blood pump
5. Turn ultrafiltration (UF) (fluid off) to 0. **Remember to turn it back on when you reconnect the patient.**

Setting up and Starting MultiFiltrate Pro with CITRATE/CiCa

Ensure you have the following:

1. 1 Litre 0.9% Nacl
2. 1500ml Sodium Citrate 4%
3. 5L Ci-Ca Dialysate bags K4 (only K2 if potassium > 6.5mmol/L) x 2
4. Calcium chloride 150mmols in 1500mls
5. Circuit
6. Red and Blue Y connectors
7. AV 1000 filter

To start:

1. Switch on machine
2. Wait for function test to be completed
3. Select new treatment
4. Select CVVHD with Ci-Ca anticoagulation
5. Confirm all conditions have been met
6. Follow step by step guide to line the machine
7. Measure post filter ionised calcium 5 minutes after starting to confirm there is adequate anticoagulation and adjust accordingly as per table 3

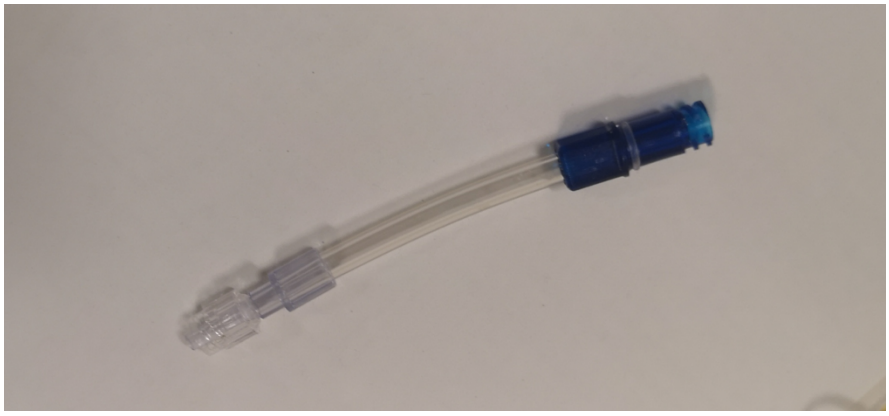
Notes

1. The citrate and calcium lines need to be clamped initially to allow a vacuum to be created. The clamps should be moved to the bag connection end of the line and clamped.
2. The citrate and calcium lines are primed first.

Multibic set up from Scratch

Equipment required

1. Standard Multifiltrate set for CVVHD
2. Multibic 4 (Multibic 0 is no longer used) Use 2 or 4 bags in total
3. 1000ml Nacl 0.9% bag for priming
4. 10 L Filtrate fluid
5. 2 x 100ml bags of Nacl 0.9% for priming the citrate and calcium lines
6. The Calcium line has a spike that will connect to the saline bag, the green citrate end has no spike and needs an adaptor it is called a HS 2000. – *the name on the packet is 'HF female-Luer Lock male'* See picture on next page.



7. When you turn on the machine the only selection you can make is CiCa CVVHD Select this and then carry on lining and priming as normal using the Multi BIC dialysate.
8. CiCa CVVHD can only be deselected when the patient is connected and the circuit detects blood. Then you need to go into MENU and select 'Switch off CiCa ' This will switch of the citrate and calcium infusion pumps. A message will appear advising you to start an alternative anticoagulation. It will also prompt to change the dialysate bags to Multibic, which can be confirmed as completed.
9. The minimum blood flow rate is 250mls and the minimum dialysate rate is 2500, there is no need for a 20:1 ratio when not using citrate i.e when using multibic.
10. Heparin via the CVVH circuit is used for anti-coagulation. See heparin anticoagulation in CVVHD guideline. It is administered through a syringe driver and not through the machine syringe selection.
11. Check APTT(R) as per heparin guideline.

Disclaimer

This protocol has been developed using input from the Fresenius protocol and from discussion with learned centres throughout the UK. As our experience with this protocol increases, changes will be made to ensure this protocol fits our patient population.

References

1. Khadzhynov D et al. Incidence and outcome of metabolic disarrangements consistent with citrate accumulation in critically ill patients undergoing continuous venovenous hemodialysis with regional citrate anticoagulation. *J Crit Care* 2014;29:265-71
2. Ci-Ca Regional citrate anticoagulation. Clinical implementation of Ci-Ca therapy protocols. Fresenius medical care.
3. Bai, M., Zhou, M., He, L. et al. Citrate versus heparin anticoagulation for continuous renal replacement therapy: an updated meta-analysis of RCTs Intensive Care Med (2015) 41: 2098.

Contacts

If you have any problems or questions regarding citrate CVVHD or this protocol please contact Oliver or Jennifer below.

- Oliver Robinson: oliver.robinson1@nhs.net (if urgent 07736285680)
- Jennifer Service: jennifer.service@nhs.net

If you have any questions about the Multifiltrate Pro machines please contact Fresenius on the numbers below.

- Fresenius MultiFiltrate Helpline: (Mon- Fri 09:00 – 17:00) **01623 445104**
- Fresenius MultiFiltrate Helpline: (Out of hours) **0870 458 7971**

PICTURE 1

Haemofiltration Recording & Fluid Prescription

	Machine ID	Kidney Batch No.	Lines Batch No.	Date & Time	
1					
2					

Blood flow (mls/min)	Dialysate flow (mls/hr)	Fluid removal (mls/hr)	Anticoagulation (citrate/heparin/other/nothing)	Prescribed by Nurse or Doctor (sign)

CiCa K4 (4 mmol/l K^+) - 5 L	Time	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	
Signature	Initials x2																
Name (PRINT)	Batch No																
Exp. Date ___/___/___																	
CiCa K2 (2 mmol/l K^+) – 5L	Time	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	
Signature	Initials x2																
Name (PRINT)	Batch No																
Exp. Date ___/___/___																	
MULTIBIC K4 (4 mmol/l K^+) - 5L	Time	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	
Signature	Initials x2																
Name (PRINT)	Batch No																
Exp. Date ___/___/___																	
SODIUM CITRATE 4% - 1.5L	Time	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	
Signature	Initials x2																
Name (PRINT)	Batch No																
Exp. date ___/___/___																	
Calcium Chloride 150mmol in 1500ml	Time	08	09	10	11	12	13	14	15	16	17	18	19	20	21	22	
Signature	Initials x2																
Name (PRINT)	Batch No																
Exp. date ___/___/___																	