The Mid Yorkshire Hospitals NHS Trust

Critical Care Protocol

Continuous Renal Replacement Therapy using Regional Citrate Anticoagulation

This protocol is intended solely for critical care personnel who have undergone the appropriate training in the use of this therapy.

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Ratified By	Same
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Introduction

Starting in January 2018, citrate is the preferred method of anticoagulation for Continuous Renal Replacement Therapy (CRRT) in the Intensive Care Unit, Mid Yorkshire Hospitals NHS Trust and should be used for the majority of patients. The machines used (Gambro Prismaflex) and the filter sets are the same as for heparin-based CRRT. However, the fluids and software are different, and the default mode for citrate in MYH is haemodiafiltration.

Calcium is required for the blood's normal clotting cascade to function. Citrate works as an anticoagulant by binding calcium in the patient's blood as it enters the filter circuit, reducing the ionised (free, or available) calcium concentration below the point at which clotting can occur. Some of the citrate-calcium complex is removed by the filter itself; additional calcium is also replaced after the blood has passed through the filter. The remaining citrate is converted to bicarbonate by the liver. These mechanisms ensure that the clotting cascade is rendered ineffective within the filter circuit, but functions normally in the patient's body, i.e. citrate anticoagulation is *regional*.

The citrate is given as pre-filter dilution (Prismocitrate 18/0), the dialysate fluid is Prism0cal B22, and the post-filter replacement is Prismasol 4. Calcium gluconate is given as replacement for the lost calcium ("calcium compensation"), at a rate which is calculated by the machine from the other flow rates.

There are a number of advantages to using citrate. Filter life is prolonged, access issues less frequent (due to lower blood flow rates used) and nursing workload reduced. Haemorrhage risk is reduced compared to heparin, and the risk of Heparin-Induced Thrombocytopenia is avoided completely.

Due to the regional nature of the anticoagulation, the CRRT may continue to run whilst procedures such as percutaneous tracheostomy are undertaken. In contrast to heparin-based CRRT, separate systemic thromboprophylaxis should be prescribed according to Trust protocol.

The major potential complications of citrate anticoagulation are hypocalcaemia and citrate accumulation.

Hypocalcaemia is common but rarely symptomatic. The protocol guides alteration of the calcium replacement infusion based upon the patient's ionised calcium (from a blood gas taken from arterial line, central line or peripheral stab) and the post-filter ionised calcium (taken from the blue port of the filter set).

Citrate accumulation is more serious but uncommon. It results from failure of the patient's liver to clear the infused citrate and is monitored with the T:I (total to ionised calcium) ratio. The protocol below details its management.

Minor complications include hypomagnesaemia (which is treated in the conventional way) and metabolic alkalosis (see advice below).

This protocol substantially reproduces the Bradford Royal Infirmary protocol, written by Dr Tom Lawton, which in turn was adapted from information provided by Gambro, Eastbourne ITU, and a local modification of the Kalmar protocol to incorporate lower flow rates. It also incorporates elements of the Salford Royal protocol.

Before starting treatment

1. Check for relative contra-indications to use of citrate

Citrate may potentially still be used in these conditions but close attention should be paid to calcium, pH, and the T:I ratio.

Increased risk of citrate accumulation (severely impaired liver or mitochondrial function)

- Severe liver failure (suggest alternate or no anticoagulation)
- Severe cardiogenic shock (suggest alternate anticoagulation)
- Severe lactic acidosis
- Ethylene glycol poisoning
- Amphetamine/MDMA poisoning
- Cyanide poisoning
- Mitochondrial cytopathies e.g. MELAS, MERRF
- HIV medication (primarily stavudine, didanosine, zidovudine)

Increased risk of hypocalcaemia (makes monitoring and adjustment more difficult)

- Rhabdomyolysis (also calcium replacement increases risk of muscle damage in survivors)
- Amphetamine/MDMA poisoning
- Acute pancreatitis
- Tumour lysis syndrome
- Toxic shock syndrome

2. Check blood results before the start of treatment:

- Total Calcium**,** Magnesium and Potassium levels
- Ensure a recent blood gas includes ionised calcium (Ca^{2+}_i or iCa^{2+})
- Haematocrit (= 100 x the PCV from the Full Blood Count)

3. Calculate total:ionised (T:I) calcium ratio - using methods described later; if greater than 2.5 discuss with medical staff.

4. Correct hypocalcaemia (ionised calcium < 1 mmol/L) – normal starting values (1-1.2 mmol/L) will make achieving stability much quicker and reduce the number of blood tests and changes needed. Give 30 mL 10% calcium gluconate over 10 mins and recheck.

Equipment needed

- 1 Kit Prismaflex ST150
- 1 CA250 Calcium line
- 1 50mL Luer lock syringe
- Y connector
- 1 bag of 5L **PRISMOCITRATE 18/0** (citrate used as pre-filter dilution)
- 1 bag of 5L **PRISM0CAL B22** (dialysate)
- 1 bag or 5L **PRISMASOL 4** for post-filter replacement
- 0.9% Sodium Chloride (priming solution) – 2000 mLs for ST150
- Calcium Gluconate 10% (5 x 10mL ampoules) - drawn up into 50 mL syringe.

Setting up and priming circuit

1. Choose the option CVVHDF
2. Choose Citrate–Calcium via Prismaflex Syringe Pump
3. Follow the installation steps on the screen.
4. Install **PRISMOCITRATE 18/0** on the white scale (PBP = Pre Blood Pump).
5. Install **PRISM0CAL B22** on the green scale. (Dialysate)
6. Install **PRISMASOL 4** on the purple scale (Replacement).
7. Prime the circuit with 2L (ST150) of 0.9% Sodium Chloride (no heparin required)
8. Install the Calcium Gluconate syringe in the Prismaflex syringe pump.

Starting parameters

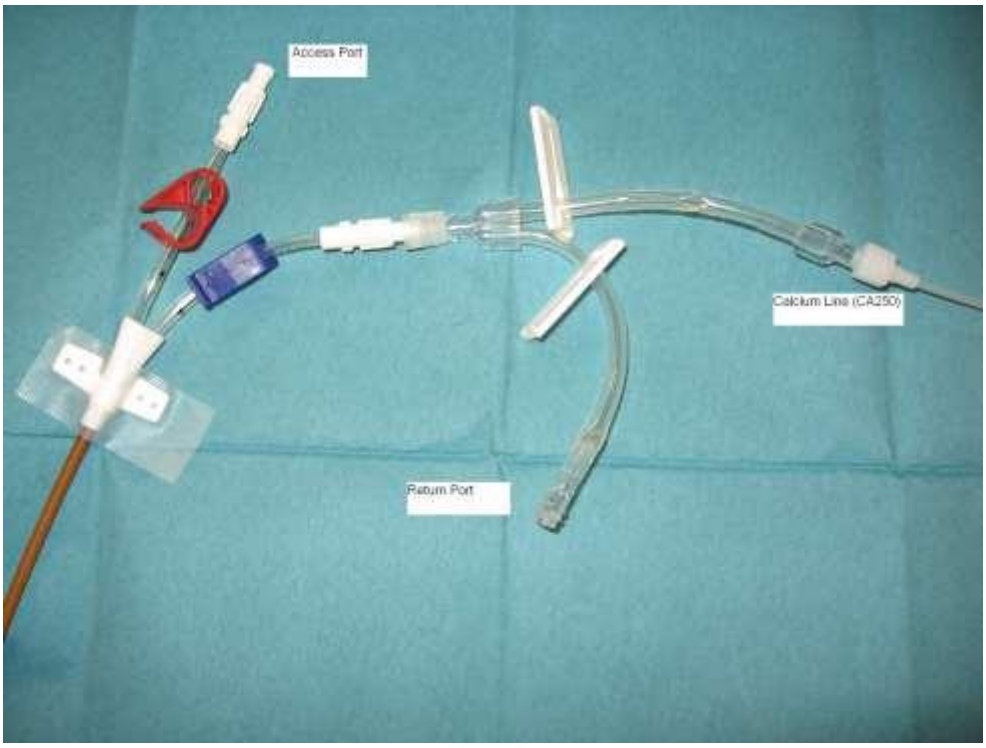
Mode: CVVHDF
Citrate dose: 3.0 mmols per litre of blood flow (the machine calculates the Prismacitrate flow rate from this)
Flow rates: SEE APPENDIX B - use Ideal Body Weight (IBW) to calculate flow rate, rounding to the nearest 10 kg.
Calcium compensation: 100% if initial patient ionised calcium 1.0-1.3. If initial patient ionised calcium > 1.3, start at 90%.
Fluid removal - as required based on the patients fluid balance - consider this as the equivalent of the patient's urine output.

Haematocrit

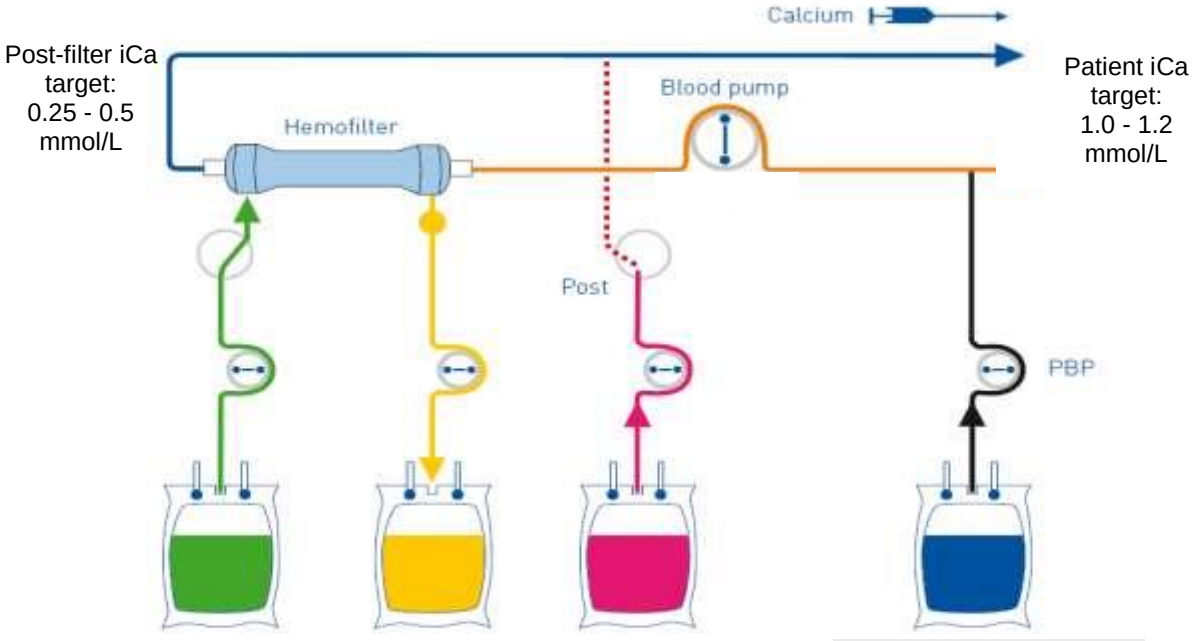
This must be checked on an up-to-date arterial blood gas (or lab sample) and entered into the Prismaflex machine. Any change in haematocrit (i.e. if transfused or given large volumes of fluid) needs to be updated on the machine. Changes in haematocrit affect the machine-calculated citrate dosing.

Connection

1. Connect Red access line to patient.
2. Connect Blue return line to one port on the Y connector.
3. Connect yellow line to effluent bag
4. Connect **CALCIUM** line to available port on the Y connector
5. Disconnect Y connector from priming bag spike and attach to patient 6. Tape calcium line to return line
7. Unclamp all lines



Please note that Gambro advise connecting the Calcium line directly to the patient's central line, and the connection to a Y-connector attached to the catheter is an unofficial procedure that has been found to have advantages. Taping the calcium line to the return line prevents inadvertent error if the return and access lines are switched (i.e. when troubleshooting access issues) – in this situation the whole Y-connector must be switched, and not just the return line.



Treatment monitoring

Once treatment has been established for one hour, make two ionised calcium checks (one from the blue port on the set and another from the patient's arterial line) and alter according to the table on the next page. Note that calcium compensation adjustments refer to changes in *percentage points*, e.g. "10% increase" from 90% gives 100%, **not** 99%.

Check both post-filter ionised calcium and patient ionised calcium **hourly** until ideal values have been achieved. Once ideal values are achieved, perform a check every **6 hours.**

If there are any changes in citrate dose or blood flow rate then patient and post-filter calcium must be rechecked in one hour.

If the patient does not have an arterial line, the patient sample should be taken from a central venous catheter. If the patient has neither arterial nor central line then a patient sample may be taken from the red port closest to the vascath; this is not ideal and may lead to abnormal values, so an arterial line should be sited if feasible. The red port on the machine is not suitable for sampling. Sampling from a Trilyse line is not appropriate as it may give abnormal values.

Repeatedly increasing requirements for calcium compensation could indicate citrate accumulation, and the T:I ratio should be checked even if within the first 6 hours. (If the patient is hypocalcaemic before filtration it is not uncommon to transiently require 130-150% calcium compensation, but this should be avoided by correcting calcium prior to initiating filtration.)

CALCIUM ADJUSTMENT PROTOCOL				
All values are for *ionised* calcium from blood gases		**FILTER VALUES** Sample from blue port on filter set		
		Filter iCa^{2+} >0.5	**Filter iCa^{2+} 0.25-0.5**	**Filter iCa^{2+} <0.25**
PATIENT VALUES Sample from arterial or central line	**Patient iCa^{2+} < 1.0**	Increase citrate dose by 0.5 mmol/L **and** increase calcium compensation by 10%	Increase calcium compensation by 10%	Decrease citrate dose by 0.5 mmol/L
		If patient Ca^{2+} <0.8, give 30 mL 10% Ca gluconate over 10 mins	**If patient Ca^{2+} <0.8, give 30 mL 10% Ca gluconate over 10 mins**	**If patient Ca^{2+} <0.8, give 30 mL 10% Ca gluconate over 10 mins**
	Patient iCa^{2+} 1.0 - 1.2	Increase citrate dose by 0.5mmol/L	**Normal Ideal Values** No changes.	Decrease citrate dose by 0.5 mmol/L
	Patient iCa^{2+} > 1.2	Decrease calcium compensation by 10%	Decrease calcium compensation by 10%	Decrease calcium compensation by 10% **and** decrease citrate dose by 0.5 mmol/L

If there are any changes in citrate dose or blood flow rate then patient and filter calcium must be rechecked in one hour.

Example 1 - patient ionised calcium 1.25, filter ionised calcium 0.35 = “Decrease calcium compensation by 10%”

Example 2 – patient ionised calcium 1.15, filter ionised calcium 0.22 = “Decrease citrate dose by 0.5 mmol/L”

Calcium T:I Ratio Monitoring – initial check after 6 hours

Divide patient's total (uncorrected) calcium by the patient's ionised calcium: the T:I ratio.

Use **Total Calcium** (**not** Adjusted or Corrected Calcium). This should be available on ICE. Divide the **Total Calcium** by the **Ionised Calcium** (from a paired ABG) using a calculator. This gives the **T:I Ratio**.

T:I Ratio Value	Action
<2.5	**Check Daily**
>2.5	**Inform doctors ASAP** **Ensure that post-filter calcium is 0.4 to 0.5 mmol/L; if it is < 0.4 mmol/L, decrease citrate dose (e.g. by 1 mmol/L) until it is 0.4-0.5 mmol/L, then check T:I ratio again. If ratio is still above 2.5 and the post-filter calcium is 0.4-0.5 mmol/L then consider stopping citrate and use an alternative anticoagulant or no anticoagulant.**

Monitoring timescale

MONITORING OF ANTICOAGULATION	Initially	And then
POST-FILTER IONISED CALCIUM (Blood Gas from circuit) Target 0.25 to 0.50 mmol/L	Hourly until stable	6 Hourly
PATIENT SYSTEMIC IONISED BLOOD CALCIUM (Blood Gas from patient) Target 1.00 to 1.20 mmol/L	Hourly until stable	6 Hourly
PATIENT TOTAL CALCIUM (see above) Target 2.20 to 2.50 mmol/L		Daily
CALCIUM T:I RATIO (Total Ca / Patient systemic ionised Ca) Target ratio <2.5	After 6 hours	Daily

Further monitoring

BLOOD GASES	REASON	Frequency
pH	To monitor acid-base balance	4-6 hourly from blood gas or more frequently as clinically indicated
Base Excess/Bicarbonate	To monitor acid-base balance	
Potassium	Monitoring for hypo or hyperkalaemia – replace if needed	
Glucose	Be aware there is no glucose in Prismocitrate 18/0	
Bicarbonate	One Citrate molecule converts to three bicarbonate molecules	

Daily monitoring

Magnesium	Urea
Phosphate	Haemoglobin
Haematocrit	Creatinine
Albumin	Sodium
Calcium (adjusted or total)	

Additional supplementation of magnesium and phosphate may be required. Please note above guidance regarding **haematocrit**, an up-to-date value must be entered on the Prismaflex machine.

Complications and trouble-shooting

(Gambro 24 hr helpline is 0808 100 3539.)

Any unexpected problems should prompt a thorough check to ensure correct setup of the circuit, fluids and filter parameters.

Hypocalcaemia

This is a potential consequence of inadequate post filter replacement. Symptoms include paraesthesia, hypotension, arrhythmias and prolonged QT. Follow the above instructions by cross referencing the patient and filter Ca^{2+}.

Citrate Accumulation

This is a potential consequence of liver failure, lactic acidosis or CRRT management error. It causes an increased anion gap metabolic acidosis and refractory hypocalcaemia. Signs of this developing are:

- An otherwise unexplained worsening metabolic acidosis (with increased anion gap)
- Rising lactate
- Persistent ionised hypocalcaemia/increasing calcium replacement requirements
- TI ratio >2.5

Six hours after initiating CRRT and then daily you must check the total Ca:ionised Ca ratio. Also check this ratio at any time if clinically concerned. This described above.

If the T:I ratio is greater than 2.5:

- Ensure all settings are correct as per the charts above, and filter setup is correct.
- Ensure post filter Ca is 0.4-0.5 mmol/l by altering the citrate dose (i.e. minimal possible citrate dose)
- Check liver function and lactate, has one of the conditions listed above been missed?
- Notify senior medical staff and consider contacting Gambro (number above).
- If this fails to correct the ratio and/or acidosis and hypocalcaemia then halt citrate anticoagulation. Either switch to heparin or use no anticoagulation – default to the non-citrate CRRT protocol.

Electrolyte disturbances

Sodium, magnesium, phosphate and potassium levels must all be monitored and replaced/controlled as needed. The replacement fluid does contain some electrolytes but additional supplementation may be required, particularly phosphate.

Inadequate clearance

Failure to clear acidosis, urea, creatinine or potassium can potentially be corrected by moving from the standard to the high dose protocol. If already on the high dose protocol

then move up the treatment chart by a weight level (i.e. 70 kg patient treated with the settings for a 80 kg patient). This ensures all flows remain correct relative to each other. This may also be indicated where clearance of large molecules (such as myoglobin in rhabdomyolysis) is required or in poisoning and overdose cases. If treating the patient based on an altered weight please document on the chart as the "treatment weight". Another option to increase clearance is to increase the replacement fluid rate (e.g. by 500 mL/h) without adjusting other flow rates.

Excessive clearance on the low dose protocol should not be a problem but can be managed by using a treatment weight that is **less** than the patient's ideal body weight.

Metabolic acidosis/alkalosis

Due to citrate's conversion to bicarbonate there are high levels of bicarbonate delivered by the citrate solution (54 mmol/L) when compared to the dialysate solution (22 mmol/L). This allows the patients metabolic control to be altered with the CRRT.

By altering the ratio of citrate to dialysate you can alter the amount of bicarbonate being delivered to the patient. Relatively more citrate solution to dialysate means more delivered bicarbonate and will push the pH up. Conversely relatively less citrate to dialysate will push the pH down.

In the event of an acidosis other causes including citrate accumulation must be assessed. Do not adjust dialysate/citrate flow in order to correct pH before the patient has initially stabilised on CRRT (e.g. a patient who is very acidotic at the time of initiation).

If the patient develops a metabolic alkalosis on CRRT (pH>7.45, BE >2) then, after assessing for other causes, you can increase the dialysate flow to the next level on the chart.

If the patient develops an increasing metabolic acidosis on the CRRT (pH<7.35, BE < -2) **and no other cause is found** then senior nursing or medical staff could consider reducing the dialysate flow to the next level on the chart. **A more straightforward solution, if clearance overall is poor, is to increase all treatment settings** (i.e. move to high dose, or increase the treatment weight if already on high dose). Separate bicarbonate supplementation can also be considered – discuss with senior medical staff.

Cessation of citrate anticoagulation

When citrate needs to be stopped due to citrate accumulation, new development of a contra-indication, or any other reason, we currently recommend that the filter blood is returned to the patient, and CRRT is restarted (if still required) using the previous MYH CRRT protocol, using either heparin or no anticoagulation.

Appendix A - Fluid composition

All in mmol/L

Prismocitrate 18/0

- Citrate 18
- Sodium 140
- Chloride 86

Prism0cal B22

- Bicarbonate 22
- Lactate 3
- Sodium 140
- Potassium 4
- Magnesium 0.75
- Chloride 120.5
- Glucose 6.1

Prismasol 4

- Bicarbonate 32
- Lactate 3
- Sodium 140
- Calcium 1.75
- Potassium 4
- Magnesium 0.5
- Chloride 113.5
- Glucose 6.1

Appendix B – Flow Settings

Use **ideal body weight (IBW)** for all filter calculations – see chart below. If height is unavailable, consider using ulnar length as per unit protocol.

Standard dose (~25 ml/kg/h)

Height (male) (m/ft)	Height (female) (m/ft)	Ideal body weight (kg)	Blood flow (mL/min)	Prismocitrate rate (mL/h) for citrate dose of 3 mmol/L	Dialysate (mL/h)	Replacement (mL/h)	Total (mL/h)	Dose (mL/kg/h)
N/A	<1.5 ≤4'11	45	70	700	450	200	1350	30
≤1.57 <5'2	1.5-1.62 *5'0-5'4*	50	80	800	500	200	1500	30
1.58-1.68 *5'2-5'6*	1.63-1.73 *5'5-5'8*	60	90	900	500	200	1600	26.7
1.69-1.79 *5'7-5'10*	1.74-1.84 *5'9-6'0*	70	100	1000	550	200	1750	25
1.8-1.9 *5'11-6'3*	≥1.85 ≥6'1	80	110	1100	600	300	2000	25
>1.9 >6'3	N/A	90	120	1200	650	400	2250	25
N/A	N/A	100	130	1300	700	500	2500	25

High dose (~35 ml/kg/h)

Height (male) (m/ft)	Height (female) (m/ft)	Ideal body weight (kg)	Blood flow (mL/min)	Prismocitrate rate (mL/h) for citrate dose of 3 mmol/L	Dialysate (mL/h)	Replacement (mL/h)	Total (mL/h)	Dose (mL/kg/h)
N/A	<1.5 ≤4'11	45	90	900	750	150	1800	40
≤1.57 <5'2	1.5-1.62 *5'0-5'4*	50	100	1000	800	200	2000	40
1.58-1.68 *5'2-5'6*	1.63-1.73 *5'5-5'8*	60	110	1100	800	200	2100	35
1.69-1.79 *5'7-5'10*	1.74-1.84 *5'9-6'0*	70	120	1200	900	350	2450	35
1.8-1.9 *5'11-6'3*	≥1.85 ≥6'1	80	130	1300	1000	500	2800	35
>1.9 >6'3	N/A	90	140	1400	1100	650	3150	35
N/A	N/A	100	150	1500	1200	800	3500	35

Use **standard dose** (25 mL/kg/h) in stable patients or those for whom fluid management is the priority. Most patients should be on the standard dose protocol after 24 hours to reduce the risk of hypophosphataemia/magnesaemia and excessive drug clearance.

Use **high dose** (35 mL/kg/h) for patients who are starting the filter urgently (eg initial therapy for those with severe sepsis, severe metabolic acidosis, hyperkalaemia). Consider reducing to standard dose once the metabolic derangement is controlled.

If standard dose is insufficient, increase to high dose.

If high dose is insufficient, either step up to the next weight band (note this option increases citrate load which increases risk of citrate accumulation), or alternatively increase the replacement flow rate to achieve a total dose closer to 45 mL/kg/h. (Total dose = citrate flow + dialysate flow + replacement flow).

Appendix C – Calcium Adjustment

<table>
<tr><th colspan="5">CALCIUM ADJUSTMENT PROTOCOL</th></tr>
<tr><th colspan="2" rowspan="2">All values are for ionised calcium from blood gases</th><th colspan="3">FILTER VALUES
Sample from blue port on filter set</th></tr>
<tr><th>Filter iCa^{2+}
>0.5</th><th>Filter iCa^{2+}
0.25-0.5</th><th>Filter iCa^{2+}
<0.25</th></tr>
<tr><td rowspan="4">PATIENT VALUES
Sample from arterial or central line</td><td rowspan="2">Patient iCa^{2+}
< 1.0</td><td>Increase citrate dose by 0.5 mmol/L and increase calcium compensation by 10%</td><td>Increase calcium compensation by 10%</td><td>Decrease citrate dose by 0.5 mmol/L</td></tr>
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<tr><td>Patient iCa^{2+}
1.0 - 1.2</td><td>Increase citrate dose by 0.5mmol/L</td><td>Normal Ideal Values
No changes.</td><td>Decrease citrate dose by 0.5 mmol/L</td></tr>
<tr><td>Patient iCa^{2+}
> 1.2</td><td>Decrease calcium compensation by 10%</td><td>Decrease calcium compensation by 10%</td><td>Decrease calcium compensation by 10% and decrease citrate dose by 0.5 mmol/L</td></tr>
</table>

If there are any changes in citrate dose or blood flow rate then patient and filter calcium must be rechecked in one hour.