Current Recommendations for Practice in Renal Replacement Therapies:

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Aims and Objectives

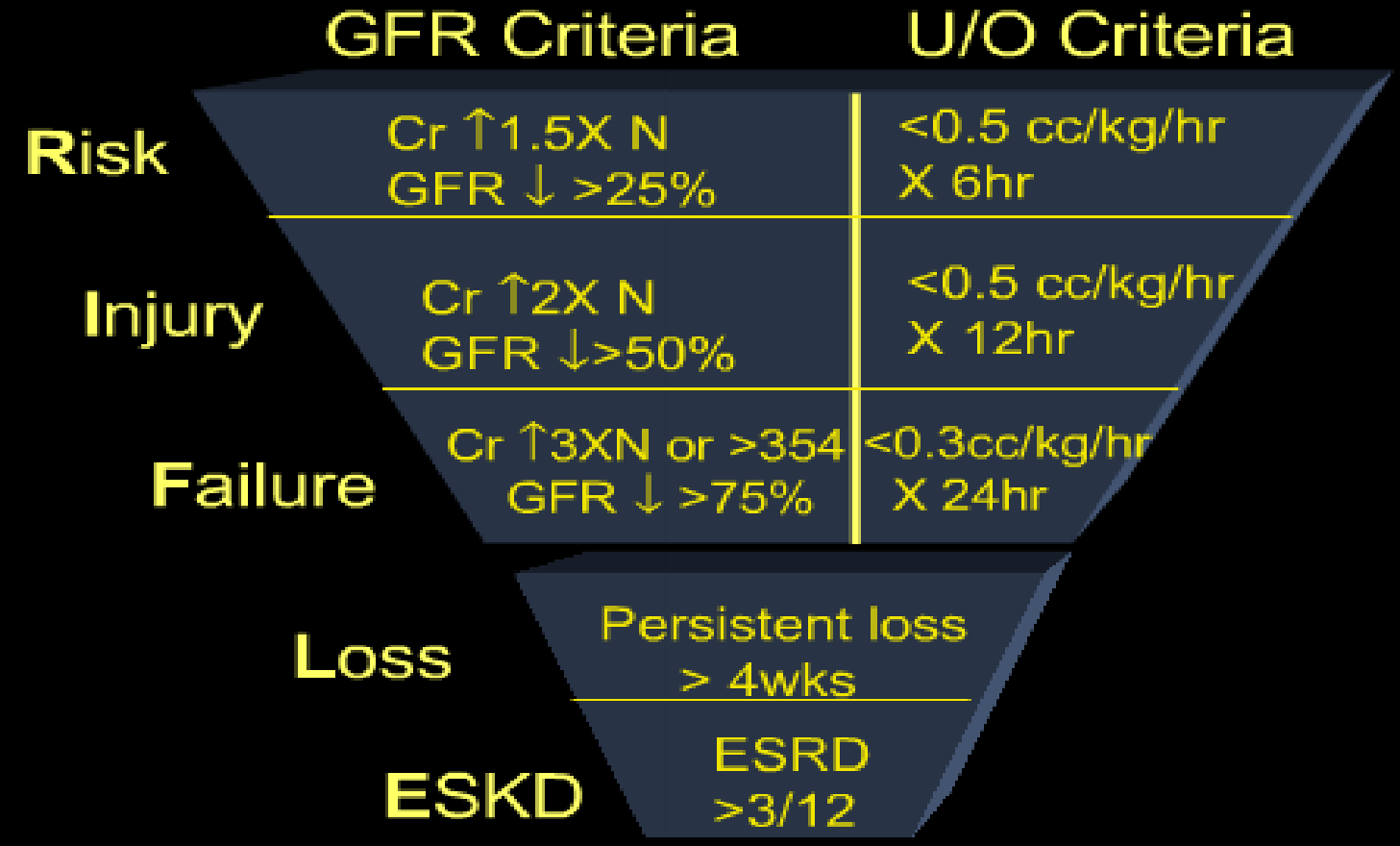
- Review goals of RRT
- Definitions of AKI
- Anticoagulants used in RRT
- Clogging versus clotting
- Optimisation of calcium dose and phosphate
- Vascath size and length
- Filter types
- What dose should be used
- Convection versus diffusion
- Is citrate suitable for all patients?

Goals of Treatment

To normalise the patient's blood chemistry by

- Correcting electrolyte imbalances
- Correcting acid base balance
- Removing metabolic waste products
- Eliminate fluid overload
- Maintain homeostasis
- Prevent further complications
- Promote favourable outcomes

Acute Dialysis Quality Initiative: **RIFLE Criteria**



KDIGO definition of AKI (2012)

- Increase in serum creatinine by ≥ 0 .3 mg/dl (≥26.5µmol/l) within 48hours: OR
- Increase in serum creatinine to ≥ 1.5times baseline, which is known or presumed to have occurred within the prior 7 days: OR
- Urine volume < 0.5mls/kg/hr for 6 hours

Stage 1

New Stages of Renal Impairment

	Serum Creatinine (SCr) Criteria	Urine output criteria
Stage 1	Increase ≥ 26µmol/L within 28 hours or increase ≥ 1.5 to 1.9 reference SCr	< 0.5 ml/kg/hr for > 6 consecutive hours
Stage 2	Increase ≥ 2 to 2.9 x reference SCr	< 0.5 ml/kg/hr for > 12 hours
Stage 3	Increase ≥ 3 x reference SCr or increase ≥ 354µmol/L or commenced on renal replacement therapy (RRT) irrespective of stage	< 0.3 ml/kg/hr for > 24 hours or anuria for 12 hours

Anticoagulants used in RRT

- **Unfractionated heparin** - the most common choice, low cost, easily available, easy to prepare and administer, established protocols for monitoring and titrating infusion, but there is and increased risk of bleeding, systemic effects leads to delays in any surgical intervention, including line replacement and there is a risk of developing heparin induced thrombocytopenia (HIT)
- **LMW heparin** – causes less bleeding episodes but may be less effective when platelet count is high
- **Epoprostenol** alone or in combination with heparin – allows heparin dose to be reduced, less incidence of bleeding but risk of hypotension, filter life may be prolonged by combination therapy
- **Heparin** (regional) – protamine counteracts anticoagulant after the filter, diligent monitoring required, adverse effects from protamine

Anticoagulants used in RRT

- **Citrate** (regional) $C_6H_7O_7$
  - good anticoagulation, works by stopping calcium from activating the clotting cascade.
  - more complicated to use because of the potential electrolyte and acid base problems it can cause

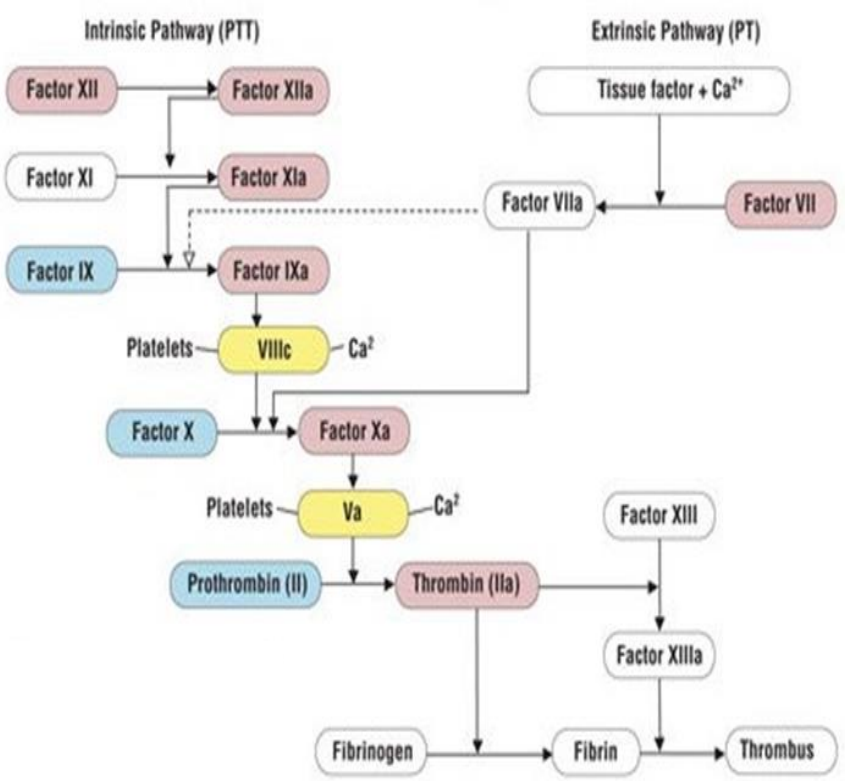


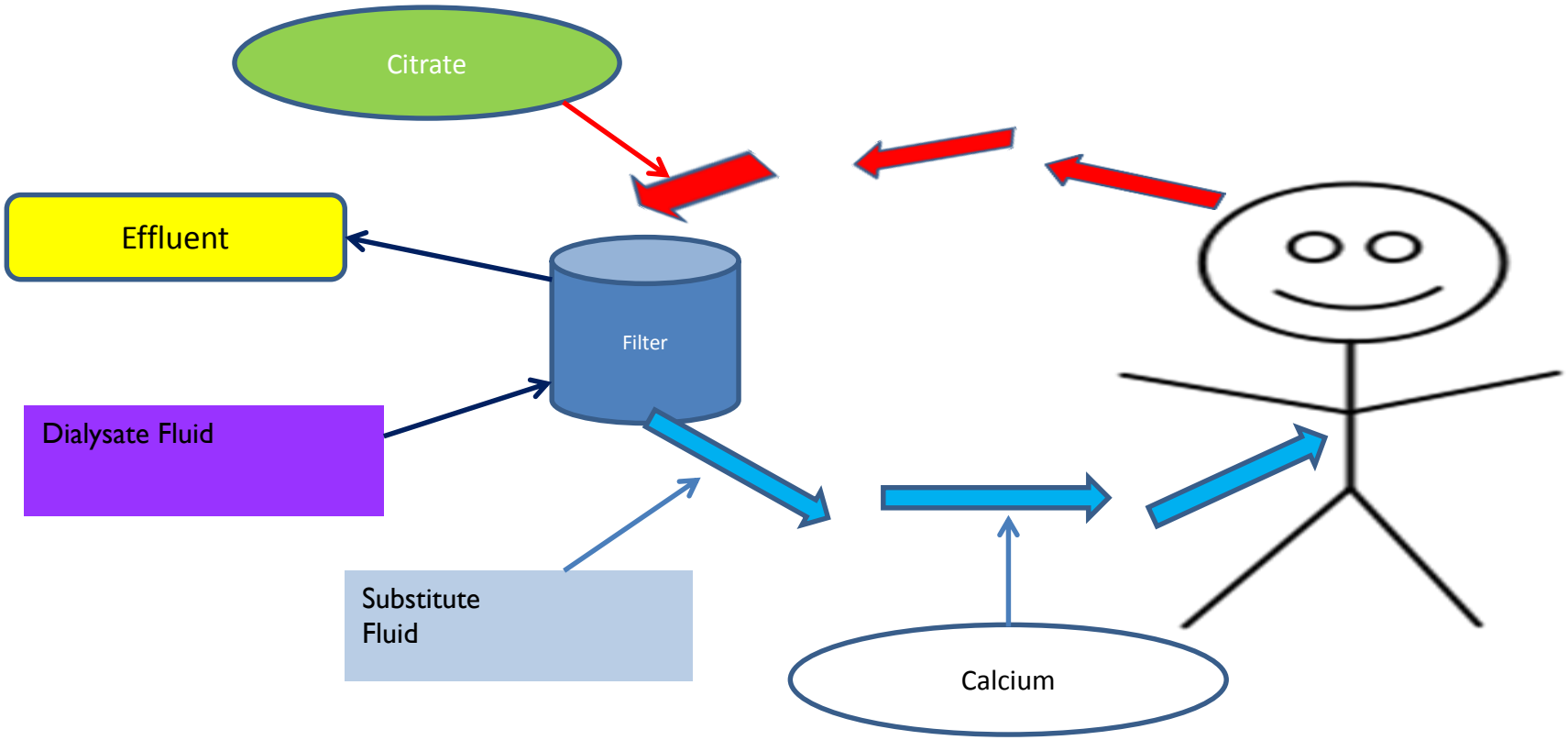
Diagram accessed from Bing.com images

Citrate anticoagulation (trisodium citrate)

- It works by binding with ionised calcium in the blood
- This reduces the amount of free ionised calcium in the blood and interrupts the clotting cascade at several stages
- To maintain a healthy balance calcium has to be replaced in the blood before returning to the patient
- Citrate clearance is mainly through convection and diffusion, although some enters the circulation
- Citrate is metabolised by the liver and skeletal muscle into bicarbonate (1:3)
- It can also affect sodium balance and acid base balance depending on the citrate load and the ability of the patient to metabolise citrate

Citrate: How it works……

Citrate Anticoagulation



Heparin or Citrate

The evidence favours citrate:

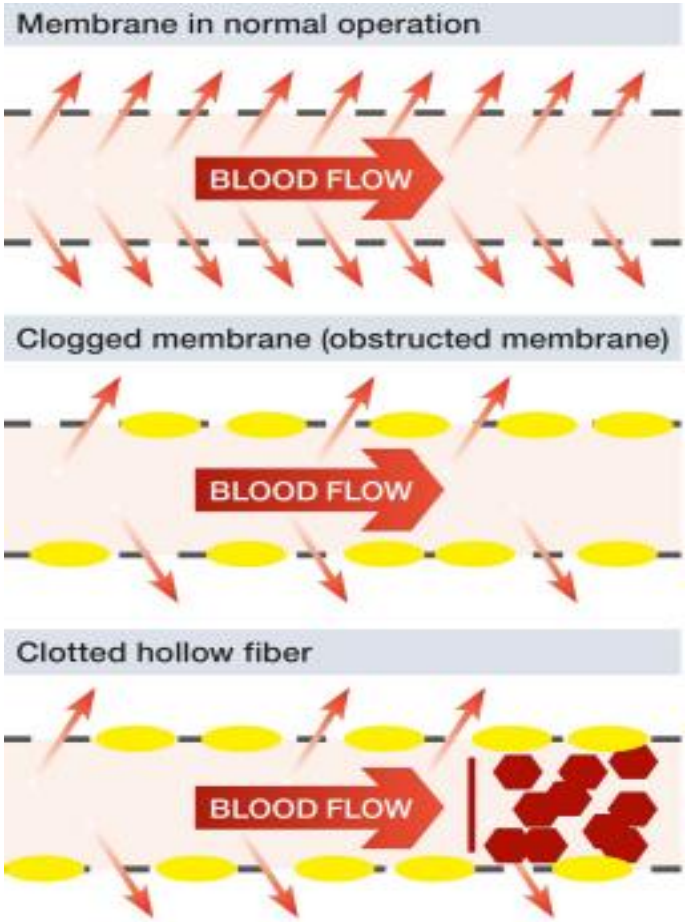
- It reduces bleeding complications
- It increases filter life span
- It reduces costs
- It reduces treatment interruptions

Schilder et al Crit Care (2014)

Stucker et al Crit Care (2015)

Gattas et al Crit Care (2015)

Clogging versus Clotting



The blood flows thorough the filter fine, but the clearances are not facilitated. The membrane is becoming clogged and the free movement of diffusion cannot occur

The blood cannot flow and clots form, the TMP may initially remain ok, but the pre filter pressure will go up first.
It can occur without clogging

Clogging Versus Clotting

- Clogging is caused by:
  - Increased protein in the plasma which accumulate inside the pores of the membrane until they totally block the pores (e.g. sepsis mediators, myoglobin)
  - Lipid rich blood (Propofol)
- Results in:
  - Impairs permeability
  - Reduced sieving coefficient
  - Metabolic alkalosis
  - Increased bicarbonate
  - Increased ionised calcium
  - Hypernatremia
- Clotting is caused by:
  - Clots in the system large enough to block the capillary fibre
- Contributing Factors
  - HIT
  - Anti thrombin 111 deficiency
- Results in
  - impaired circulation

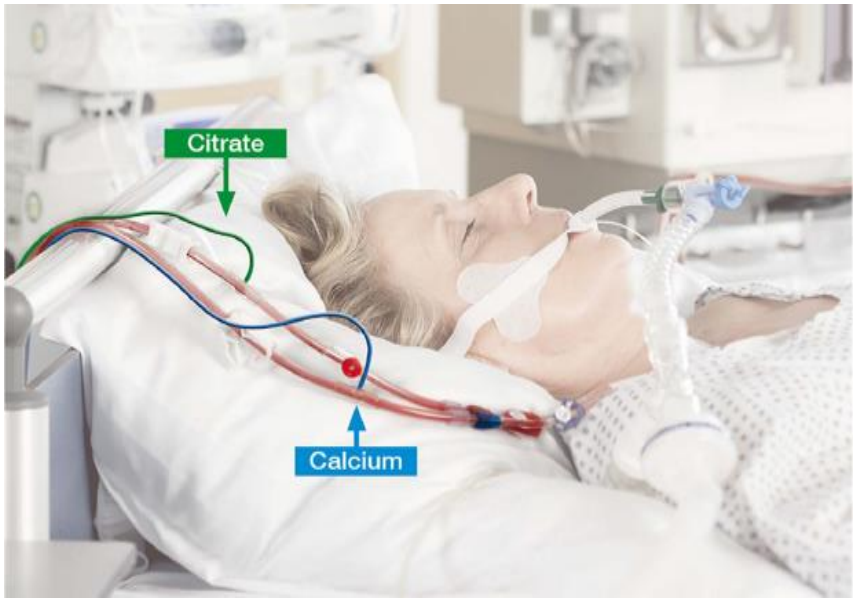
Clots in the Arterial and Venous bubble chamber

These are due to turbulent blood flow caused when the fluid levels in the bubble chambers are not appropriately filled

It is recommended to fill these chambers at least 1-2cm from the top to allow blood to flow freely out of the chamber, and allow space for any air bubbles to collect

Clotting in lines

- Clots will still occur in the lines:
  - In the access line before the citrate is added
  - In the return line after the calcium is added



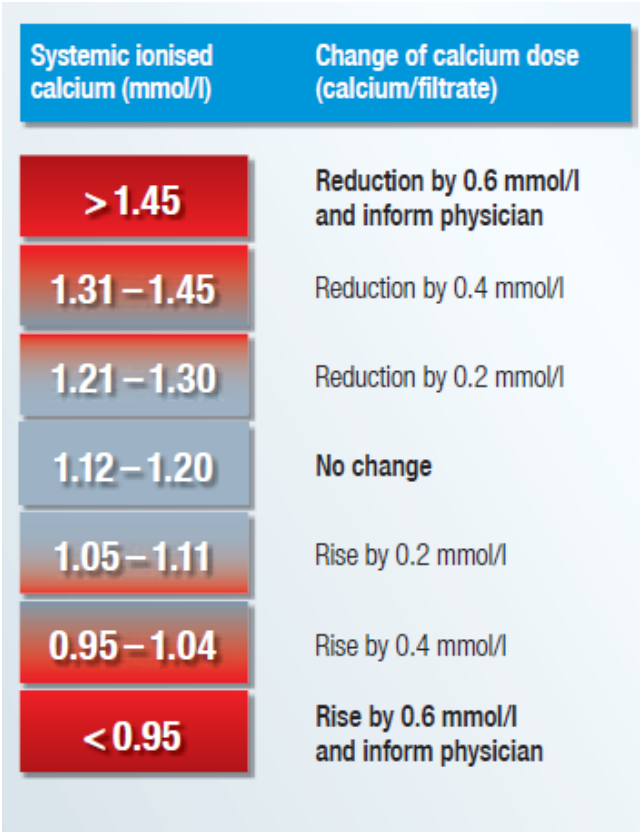
Correcting Calcium Levels

- Low levels of ionised calcium MUST be corrected prior to commencing Ci Ca haemofiltration
- Administered IV bolus of calcium gluconate/chloride
- Change starting rate of calcium according to level of ionised calcium

Systemic iCa2+ (mmol/L)	< 1.01	1.01 - 1.11	1.12 - 1.20	1.21 - 1.45	> 1.45
Pre-treatment with calcium Chloride	Yes	Yes	No	No	No
Starting dose Calcium Chloride (mmol/L)	2.0	1.9	1.7	1.5	1.4
Check first systemic iCa^{2+} and review calcium dose after	2 hours	6 hours	6 hours	6 hours	6 hours

Correcting and Maintaining Calcium Levels

Company protocol: checks repeated 6 hourly

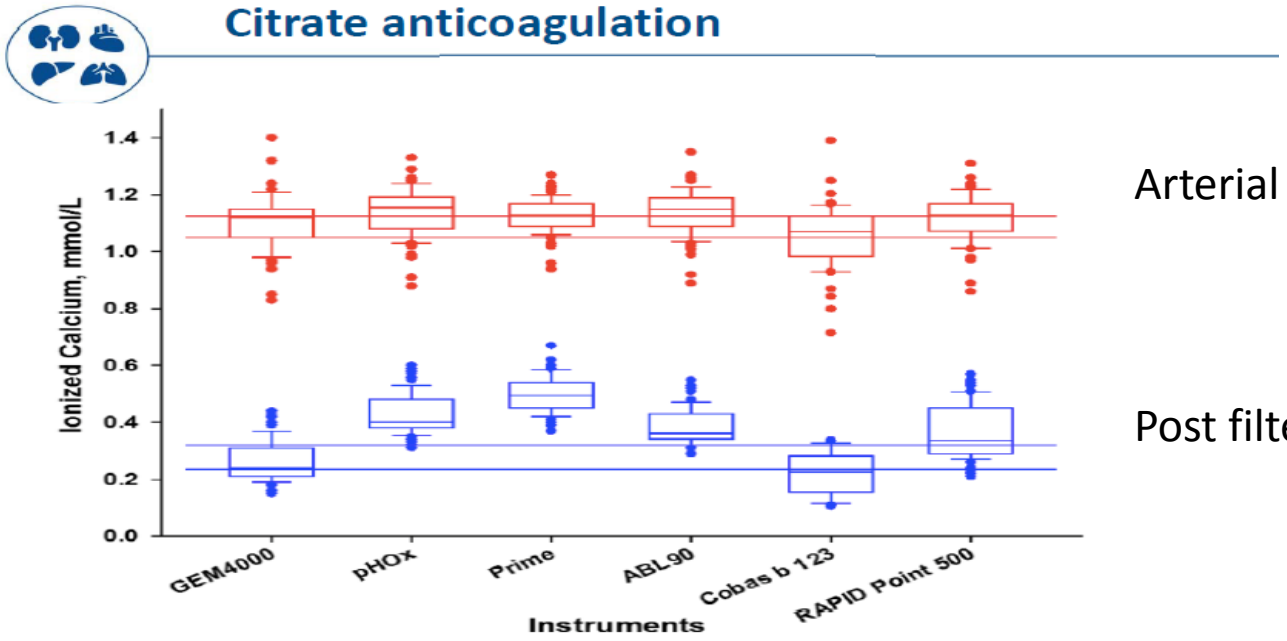


Systemic ionised calcium (mmol/l)	Change of calcium dose (calcium/filtrate)
>1.45	Reduction by 0.6 mmol/l and inform physician
1.31–1.45	Reduction by 0.4 mmol/l
1.21–1.30	Reduction by 0.2 mmol/l
1.12–1.20	No change
1.05–1.11	Rise by 0.2 mmol/l
0.95–1.04	Rise by 0.4 mmol/l
<0.95	Rise by 0.6 mmol/l and inform physician

Adapted Protocol

Systemic iCa^{2+} (mmol/L)	Change of calcium dose (calcium/filtrate)	Check systemic iCa^{2+} and review dose after
>1.35	Reduce by 0.4 mmol/L Inform Consultant ICU	6 hours
1.21-1.35	Reduce by 0.2 mmol/L	6 hours
1.12-1.20	No change Target range	6 hours
1.00-1.11	Increase by 0.2 mmol/L	6 hours
<1.00	Increase by 0.4 mmol/L Inform Consultant ICU	2 hours

Measurement of calcium



Arterial sample

Post filter sample

Some ABG machines designed not to give correct values

- post filter ionised calcium could be under or over estimated
- majority more accurate for measuring arterial ionised calcium

(GEM 4000 most accurate)

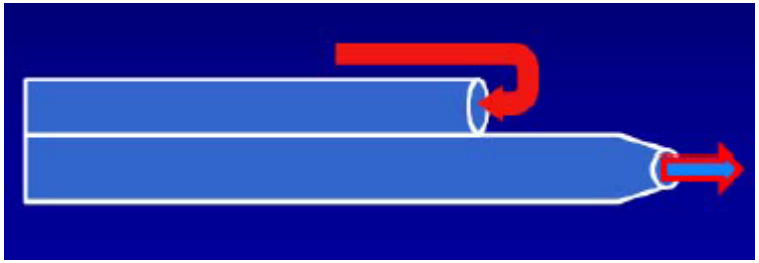
Schwarzer P et al (2015)

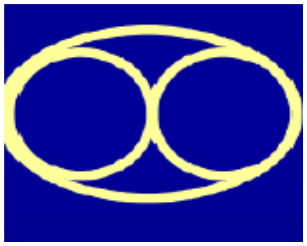
Correcting and maintaining Phosphate levels

- Phosphate free Ci Ca dialysate leads to low levels of serum phosphate as the phosphate is diffused out, this then requires replacing with either potassium acid phosphate of phosphate polyfusers at an extra costs and workload
- Ci Ca Plus© dialysate bags contains 1.25mmols/L, this helps to maintain serum phosphate levels and reduces cost and workload

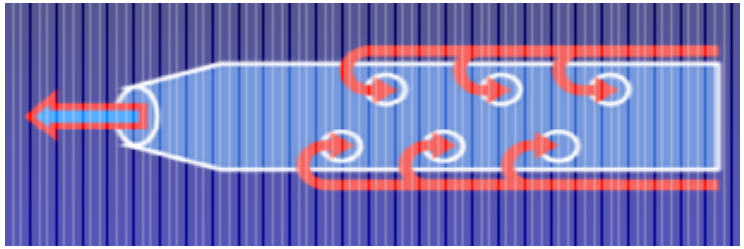
Vascath Type

Shotgun 13.5 FG





Coaxial 12 FG



Evidence recommends shot gun over coaxial

Not recommended to swap ports with shot gun vascath

Huriaux et al Anaest Crit care Pain Med 2017

Vascular Access Length

Preferential insertion site of RRT catheter and corresponding catheter length.

	Insertion location	Catheter length
1	Right internal jugular	15 cm
2	Right or left femoral	25 cm
3	Left internal jugular	20 cm
4	Dominant limb sub-clavian	Right: 15–20 cm, left: 20 cm
5	Non-dominant limb sub-clavian	Right: 15–20 cm, left: 20 cm

Evidence recommends femoral or right internal jugular and avoiding left internal jugular or subclavian KDIGO guidelines (2012)

Filter type: AV1000s versus EMIC 2

The Ultraflux® filters contain a Fresenius Polysulfone® membrane specifically developed for continuous renal replacement therapy.
Substances with a molecular weight of up to approximately 30kD can be eliminated.
Plasma proteins like albumin, other large molecules and cellular blood constituents are retained.
The filtration characteristics of this membrane come close to the natural human kidney's function.
The larger the exchange surface the better the middle size solute clearance in diffusive therapies

Properties of AV1000s:

- Effective surface area of 1.8m^2
- Blood volume 130mls
- Wall thickness/inner diameter 35/220µm

Filter type: AV100s versus EMIC 2

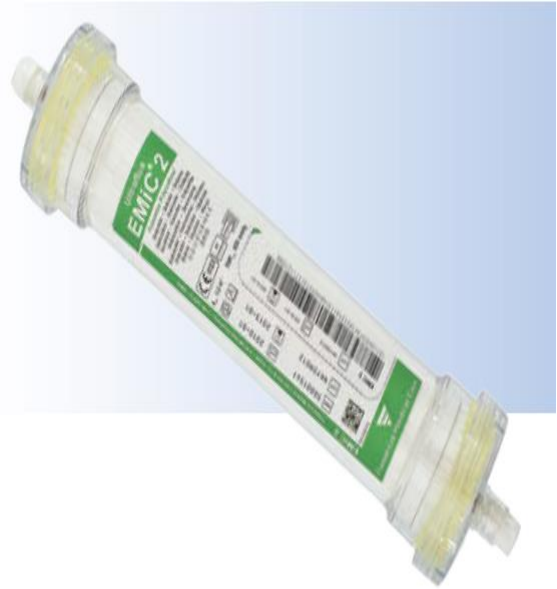
- **E**nhanced **M**iddle Molecule **C**learance – comparable to CVVH
- Substantially stable albumin levels
- Reliable citrate anticoagulation
- High efficacy with low blood flows
- multi**Filtrate** Ci-Ca®: integrated citrate and calcium management

Patients with elevated concentrations of middle molecules

- High concentration of myoglobin due to rhabdomyolysis
- Cytokines, interleukins and other factors in septic patients (studies still have to demonstrate a better outcome)

Patients with high bleeding risk and HIT

- Acute bleeding or high bleeding risk due to haemorrhage, trauma or surgery
- Heparin-induced thrombocytopaenia (HIT II) where citrate is used in combination with the required systemic anticoagulation



What dose should you use

All our patients are started on a weight related dose initially 35mls/kg/hour, although as long as a 20:1 dialysate to blood flow rate is maintained that is acceptable

Body Weight	Dialysis Solution Flow	Blood Flow	Citrate Dose	Calcium Dose
50 - 59 kg	2000 ml/hr	100 ml/min	4.0 mmol/L	1.7 mmol/L
60 - 69 kg	2200 ml/hr	110 ml/min	4.0 mmol/L	1.7 mmol/L
70 – 79 kg	2600 ml/hr	130 ml/min	4.0 mmol/L	1.7 mmol/L
80 – 89 kg	3000 ml/hr	150 ml/min	4.0 mmol/L	1.7 mmol/L
90 – 99 kg	3200 ml/hr	160 ml/min	4.0 mmol/L	1.7 mmol/L
>100 kg	3600 ml/hr	180 ml/min	4.0 mmol/L	1.7 mmol/L

It is now recommended start rates of 25mls/kg/hr

	Default Regime (Approx. 25 mL/kg/hr)				
Adjusted Body Weight	<60 kg	60-69 kg	70-79 kg	80-89 kg	>90kg
Dialysate Flow	1400 mL/h	1600 mL/h	1800 mL/h	2000 mL/h	2200 mL/h
Blood Flow Rate	70 mL/min	80 mL/min	90 mL/min	100 mL/min	110 mL/min

What dose should you use

Doses of 35mls/kg/hr should only be used if you need to drive the patient harder

	Enhanced Regime (Approx. 30-35 mL/kg/hr)				
Adjusted Body Weight	<60 kg	60 – 69 kg	70-79 kg	80-89 kg	>90 kg
Dialysate Flow	1800 mL/h	2200 mL/h	2400 mL/h	2800mL/h	3000 mL/h
Blood Flow Rate	90 mL/min	110 mL/min	120 mL/min	140mL/min	150 mL/min

- Severe sepsis / multiple vasopressors
- Metabolic acidosis(PH <7.2, BE <-10)
- Hyperkalaemia
- Myoglobinemia / Rhabdomyolysis
- Inadequate clearance
- Poisoning

Convection versus Diffusion

- CVVH
  - High blood flow required
  - Increased risk of filter clotting/clogging
  - Increased risk citrate load
- CVVHD
  - Lower blood flow required, reduces citrate load
  - Less risk of filter clogging
  - Diffusion allows for greater removal of CiCa complexes, allowing it to be used in patients in whom citrate would be contraindicated
- Overall
  - No significant differences between the two
  - Similar removal rates of small and middle molecular weight solutes
  - CVVHD warrants longer CRRT session than CVVH

Convection versus Diffusion

	CVVHD	CVVH
Mortality	=	=
Small molecules clearance	+	+
Large molecules clearance	+ – (depends on membrane permeability)	+
Hemofilter Life	+ +	+
Citrate Load	+ Low Q_B	– Clearance depends on Q_B
Nurses Workload	+	–
Costs	+	–

When to start?

- Early RRT does not appear to cause harm overall
- Severe AKI, sepsis and fluid overload /ARDS – filter early
- AKI and hepatic failure/transplant- filter early

Citrate Overload

- More risk of citrate overload when using CVVH as opposed to CVVHD
- Associated with a metabolic alkalosis
- Citrate is being metabolised in these circumstances
- Normal T:I ratio
- Common occurrence , but easy to deal with
- Caused by excessive intake or inadequate clearance
- Treatment involves reducing the blood flow and/or increasing the dialysate flow rate

Citrate Accumulation

4 key factors indicating citrate intolerance are:

- Decreasing ionised calcium levels due to citrate accumulation
- Decreasing levels of bicarbonate (metabolic acidosis)
- Increasing levels of total calcium >3 mmols/L
- T : I ratio >2.25

Citrate accumulation:

- Can be lethal, but is rare
- Treatment involves reducing blood flow and/or increasing dialysate flow rates
- Change antiocoagulant

High lactate and citrate anticoagulation

Comparison of patients with normal lactate levels and those with elevated lactate levels prior to commencement of CiCa RRT in relation to citrate accumulation

- Approximately 1% of patients with normal lactate developed citrate accumulation
- Approximately 3% of patients with moderate hyperlactaemia (2-4 mmols/L) developed citrate accumulation
- Approximately 6% of patients with severe hyperlactaemia (>4mmol/L) developed citrate accumulation
- T:I ratio main marker of citrate accumulation and predictor of mortality (>2.25)

Khadzhynov et al (2017)

Citrate is suitable for all

As long as:

- use lowest blood flow possible to reduce citrate load
- use a high dialysate flow to increase citrate clearance
- close citrate monitoring of T:I ratio
- lactate monitoring to access for Kreb's cycle alteration
- reduce blood flow +/- increase dialysate flow at first signs of a citrate accumulation
- if no improvement, STOP citrate and change to another anticoagulant
- all staff involved in citrate anticoagulation should be trained in its use

Summary and Conclusions

- New KDIGO definitions of AKI
- Citrate superior to heparin as an anticoagulant during CRRT
- Differences between clogging and clotting
- Correction of ionised calcium and phopshate
- Discussed vascath and filter types and recommended insertion sites
- Recommended dosing according to patient need
- Best modalities- convection versus diffusion
- Citrate overload versus citrate accumulation
- Citrate is suitable for all patients with appropriate care and monitoring

References

- Beck J. (2019) Timing and Dosing in Renal Replacement Therapy
- Beck J (2019) Lactate and CiCa RRT

Consultant Leeds Unpublished presentations Fresenius CiCa Masterclass 13 03 2019

- Branfiled P (2019) 7 Things I have learnt with usig CiCa Multifiltrate

Plymouth Unpublished presentation Fresenius CiCa Masterclass 13 03 2019

- Charlton M (2019) The interesting and the unusual

Nurse Educator Bath Unpublished presentation Fresenius CiCa Masterclass 13 03 2019

- Dalhuisen A et al (2017)Comparing CVVH with CVVHD during citrate anticoagulation in ICU patients. Netherlands Journal of Critical Care March 2017
- Gatta D.J et al (2015) A randomised controlled trial of regional citrate versus regional heparin anticoagulation for continuous renal replacement therapy in critically ill adults Crit Care Med 2015 Aug; 43 (8) 1622-9

References

- Friedrich J.O et al (2012) Heamofiltraion compared to haemodialysis for acute kidney injury: systematic review and meta analysis Crit Care 16 R146 http://ccforum.com.content/16/4/R146
- Huriaux L et al (2017) Haemodialysis catheters in the intensive care unit Anaest Crit Care Pain Med Vol 36 Issue 5 313-319
- KDIGO (2012) Clinical Practice Guideline for Acute Kidney Injury Kidney International Supplement Vol 2 Issue 1 March 2012
- Khadzhynov et al (2017) Hyperlactatemia, Lactate Kinetics and Prediction of citrate accumulation in critically ill patients undergoing continuous renal replacement therapy with citrate anticoagulation Critical Care Medicine Vol 45 Issue 8 pp e941-946
- Lui C et al (2016) Regional citrate versus heparin anticoagulation for CRRT in critically ill patients : a meta analysis with trial sequential analysis of RCT Critical Care 2016 20:144

References

- Monard C (2019) CRRT with citrate anticoagulation: Convection or diffusion

Intensive Care and Anaesthesiology Lyon , France Unpublished presentation Fresenius CiCa Masterclass 13 03 2019

- Ricci. Z et al (2006) Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion Critical Care 2006 10: R67
- Schilder L et al (2014) Citrate anticoagulation versus systemic heparinisation in CVVH in critically ill patients with acute kidney injury : a multicentre randomised clinical trial Critical Care 2014 18:472

http://ccforum.com/content/18/4/472

- Schwarzer P et al (2015) Discrepant post filter ionised calcium concentration by common blood gas analysers in CRRT using regional citrate anticoagulation Critical Care 2015 19:321

References

- Stucker F et al (2015) Efficiency and safety of citrate based anticoagulation compared to heparin in patients with acute kidney injury requiring continuous renal replacement therapy : a randomised controlled trial Critical Care 2015 19:91