Dialysis: An Update on Citrate Anticoagulation:

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Aims and Objectives

- To give a brief overview of renal impairment, the different types of renal replacement therapies (RRT) available and the goals of RRT treatment
- Discuss why anticoagulation is necessary and what the current available options are
- Explain how citrate works, including its pros and cons
- How the therapy can be manipulated to manage acid base balance disturbances and electrolyte imbalances
- Advantages of citrate anticoagulation
- Recognising citrate intolerance and how to manage it

Diagnosis of Renal Impairment

RIFLE criteria

- **R**isk: creatinine greater than 1.5 times normal value, GFR reduced by 25% , urine output less than 0.5mls/kg/hr for 6 hours
- **I**njury :creatinine greater than 2 times normal value, GFR reduced by 50% , urine output less than 0.5mls/kg/hr for 12 hours
- **F**ailure creatinine greater than 3 times normal value(or greater than 354), GFR reduced by 75% , urine output less than 0.3mls/kg/hr for 24 hours
- **L**oss: persistent loss for more than 4 weeks
- **E**nd stage kidney disease: end stage renal disease for more than 3 months

Goals of Treatment

To normalise the patient's blood chemistry by

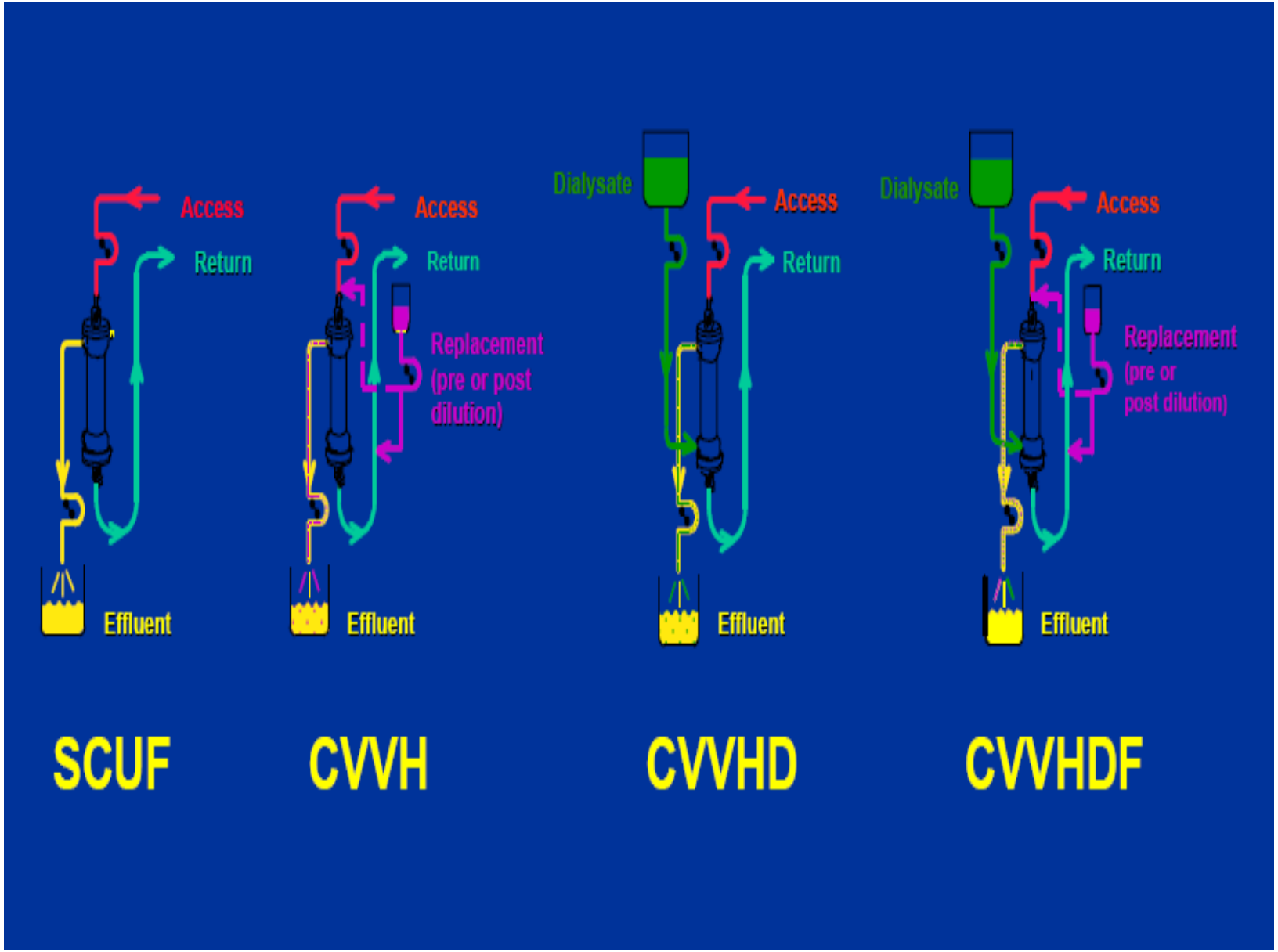
- Correcting electrolyte imbalances
- Correcting acid base balance
- Removing metabolic waste products (+drugs)
- Eliminate fluid overload
- Maintain homeostasis
- Prevent further complications
- Promote favourable outcomes (MOF)

Continuous versus intermittent

- With CRRT, volume control is continuous and immediately adaptable to the changing clinical circumstances
- Uraemic control is vastly superior with CRRT
- CRRT offers more rapid improvement and control of metabolic acidosis and reliable control of phosphate levels
- CRRT is mandatory in all patients at risk of or who have increased ICP

Types of Renal Replacement Therapy

- **SCUF –** slow continuous ultrafiltration
- **CVVH** - continuous venovenous hemofiltration
- **CVVHD** - continuous venovenous hemodialysis
- **CVVHDF** - continuous venovenous hemodiafiltration (combination of CVVH and CVVHD)
- **SLEDD** - Sustained low efficiency daily dialysis
- **PD** - peritoneal dialysis



Gambro renal products accessed from Bing.com images

Anticoagulation

- The coagulation cascade is activated as blood comes into contact with the extra-corporeal circuit
- Anticoagulation is required to
  - extend filter life and allow it to run continuously
  - improve filtration fraction and clearance characteristics
- Some patients with deranged clotting function may be filtered safely without anticoagulation, preferably using pre-dilution CVVHF

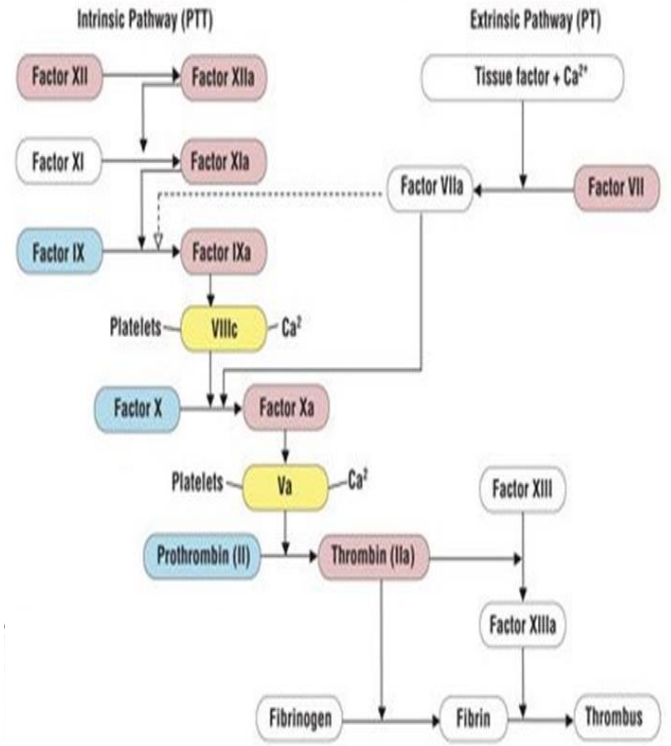


Diagram accessed from Bing.com images

Aim of Anticoagulation

- To maintain a high anticoagulation effect in the extracorporeal circuit whilst not causing excessive clotting times in the patient
- To preserve filter performance
- To increase circuit survival
- To prevent loss of blood in the circuit

Impact of Filter Clotting

- CRRT is only continuous if the anticoagulation is adequate
- Wasted nursing time, resetting up filters
- Detrimental to patient, due to the down time from treatment.
- Increase in cost.
- Inadequate treatment.

Maintaining Filter Life

Consider several factors

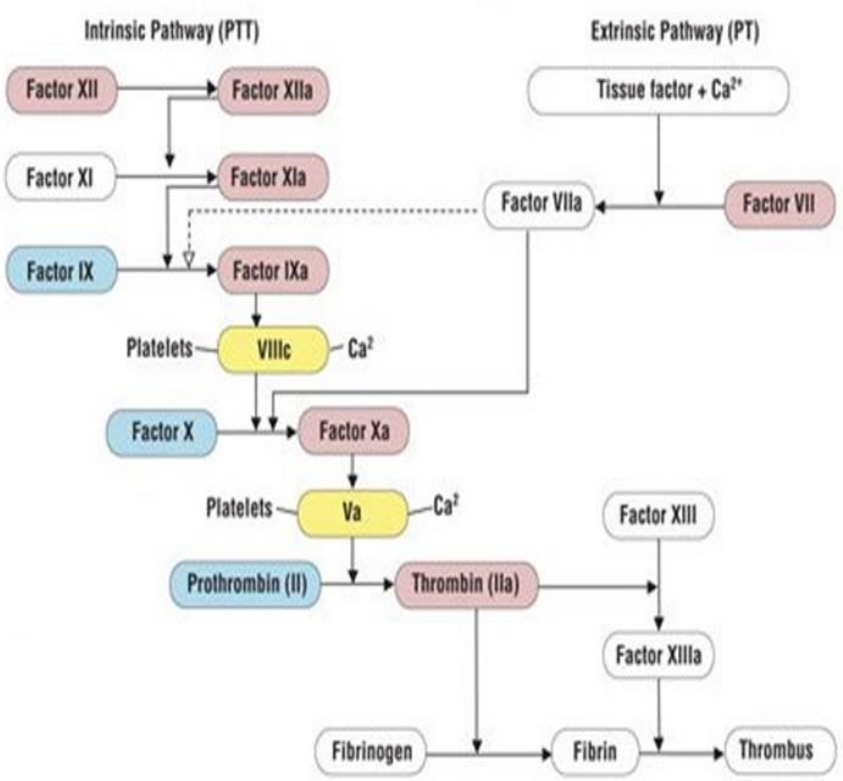
- Access
- Blood Pump Speed
- Pre v Post dilution
- Anticoagulation

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

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



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Anticoagulants used in RRT

- **Heparin** (regional) – protamine counteracts anticoagulant after the filter, diligent monitoring required, adverse effects from protamine

- Evidence suggests that citrate anticoagulation increase filter life when compared to heparin (Monchi et al 2004)

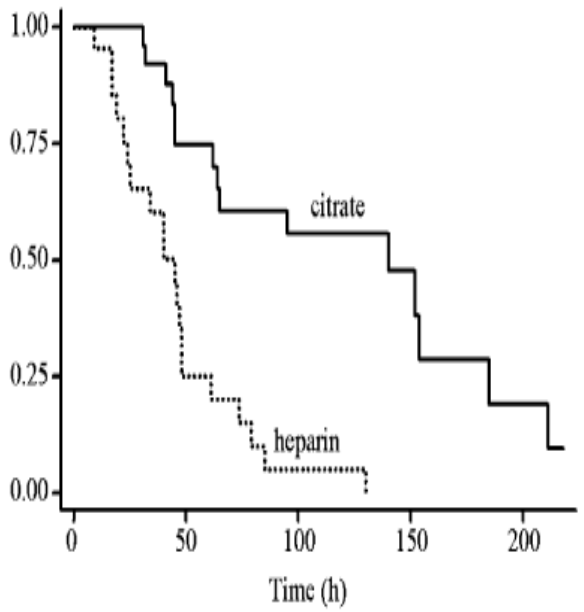


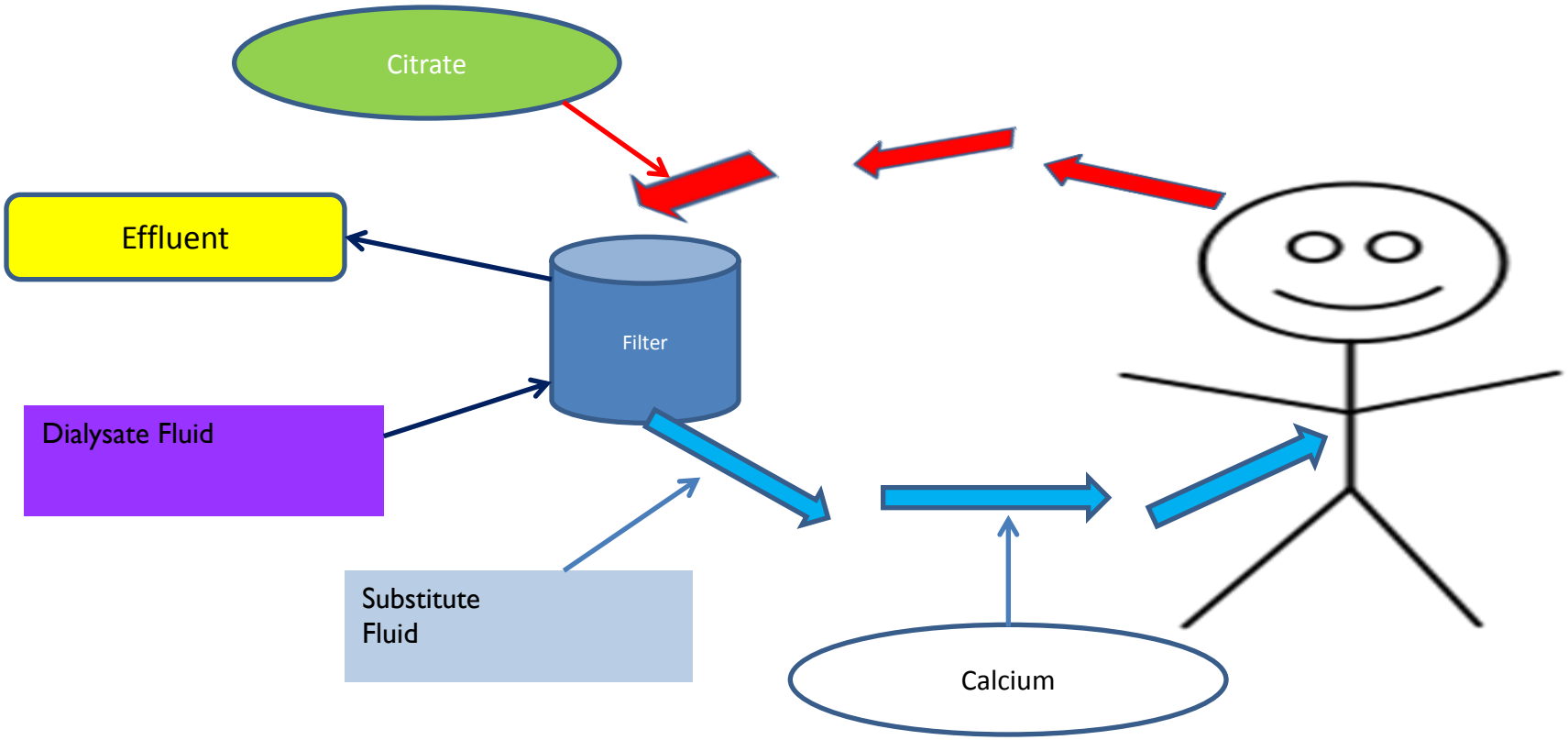
Fig. 1 Kaplan-Meier curves of time to spontaneous failure of the hemofilters, according to the anticoagulation used ($p<0.0001$)

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



Citrate:

- Pros
  - No systemic anticoagulation
  - Can be used in most patients
  - Clear Protocols for monitoring
  - Increases filter life considerably when compared to Heparin

    (Monchi et al 2004 & Kutsogiannis et al 2005)
  - Benefits of re-circulation

- Cons
  - More complicated system to manage with complex protocols
    - Citrate and calcium infusions required
  - Potential to cause:
    - Electrolyte imbalance
      - hyper/hypo calcaemia
      - hypophosphataemia
      - hypomagnesaemia
      - hypernatraemia
  - The way citrate is metabolised can cause either:
    - Metabolic acidosis
    - Metabolic alkalosis

Management of Potential Electrolyte Imbalances

- Dialysate and replacement fluid contains lower sodium levels due to the sodium load in the citrate, still a risk of hypernatreamia
- Metabolism of citrate to bicarbonate increases risk of metabolic alkalosis, therefore less HCO_3 in dialysate fluid
- No phosphate in standard bags of dialysate and replacement fluid, therefore risk of hypophosphateamia . Can use K4 plus or K2 plus
- Calcium levels affected by chelation, low levels to be replaced with calcium gluconate before and during treatment
- Magnesium levels can be affected by chelation also, low levels to be corrected with magnesium sulphate

Citrate anticoagulation: management

- The dialysate and blood flow must be maintained at a 20:1 ratio, unless adjusting for acidosis or alkalosis
- Dialysate/replacement fluid rates based on 35ml/kg/hour
- Maintaining ratios for blood flow and replacement fluid in CVVHDF (1:10)
- The citrate dose is adjusted according to post filter levels of ionised calcium
- The calcium dose is adjusted according to systemic levels of ionised calcium
- Clear protocols are devised to direct the practitioner
- Hypocalcaemia MUST be corrected prior to commencement of treatment

Dialysate	Blood flow
2000mls/hr	100 mls/min
2200 mls/hr	110 mls/min
2600 mls/hr	130 mls/min
3000 mls/hr	150 mls/min
3200 mls/hr	160 mls/min
3600 mls/hr	180 mls/min

Citrate	Calcium
4 mmols/l	1.7 mmols/l

Citrate anticoagulation: management

- Appropriate interventions to manage metabolic acidosis without citrate intolerance
  - Increase blood flow to increase amount of citrate added
  - Reduce dialysate, to decrease the amount of buffer bases lost through diffusion
- Appropriate interventions to manage metabolic alkalosis
  - Reduce blood flow to decrease the amount of citrate added
  - Increase dialysate flow to increase the amount of buffer base removed by diffusion

Advantages of Citrate anticoagulation

- As there is no systemic anticoagulation effects:
  - Patients can undergo invasive procedures such as central or arterial line insertion, whilst the citrate is still running
  - Filter blood can be returned to the patient and the filter circuit re circulated for up to 4 hours whilst the patient leaves the unit to undergo surgical intervention, CT scans or x rays and this can then be re connected to the patient on their return, no more stopping and re setting up the circuit

Citrate Intolerance

- 3 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

    (T : I ratio >2.5)
- In these circumstances the citrate dose needs to be reduced, this can be done by:
  - Adjusting the no change range for post ionised calcium
  - Reducing the blood flow in CVVHD only
  - Administering bicarbonate to correct the acidosis

If the citrate intolerance is unable to be corrected the citrate anticoagulation has to be deselected and replaced with another suitable anticoagulant

CVVHD/CVVHDF without citrate

- Calcium free dialysate **MUST** to be changed to Multi Bic 2 or 4
- Alternative anticoagulation has to used and titrated accordingly
  - Heparin
  - Epoprostenol

Summary and Conclusions

- Despite the fears and complications identified in the literature when using citrate anticoagulation, it is simple and easy to use **IF**:
  - There are clear protocols and guidelines to titrate the calcium and citrate and set the fluid and blood flow rates
  - The dialysate and replacement fluid used are specifically designed to minimise the risk of complications associated with citrate anticoagulation
  - There is appropriate training of clinical staff

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