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

<table>
<thead>
<tr>
<th></th>
<th>GFR Criteria</th>
<th>U/O Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk</strong></td>
<td>Cr ↑1.5X N</td>
<td>&lt;0.5 cc/kg/hr</td>
</tr>
<tr>
<td></td>
<td>GFR ↓ &gt;25%</td>
<td>X 6hr</td>
</tr>
<tr>
<td><strong>Injury</strong></td>
<td>Cr ↑2X N</td>
<td>&lt;0.5 cc/kg/hr</td>
</tr>
<tr>
<td></td>
<td>GFR ↓ &gt;50%</td>
<td>X 12hr</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>Cr ↑3XN or &gt;354</td>
<td>&lt;0.3 cc/kg/hr</td>
</tr>
<tr>
<td></td>
<td>GFR ↓ &gt;75%</td>
<td>X 24hr</td>
</tr>
<tr>
<td><strong>Loss</strong></td>
<td>Persistent loss &gt; 4wks</td>
<td></td>
</tr>
<tr>
<td><strong>ESKD</strong></td>
<td>ESRD &gt;3/12</td>
<td></td>
</tr>
</tbody>
</table>
KDIGO definition of AKI (2012)

- Increase in serum creatinine by $\geq 0.3 \text{ mg/dl}$ ($\geq 26.5 \mu\text{mol/l}$) within 48 hours: OR
- Increase in serum creatinine to $\geq 1.5$ times baseline, which is known or presumed to have occurred within the prior 7 days: OR
- Urine volume $< 0.5 \text{ mls/kg/hr}$ for 6 hours

Stage 1
## New Stages of Renal Impairment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum Creatinine (SCr) Criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Increase $\geq 26\mu$mol/L within 28 hours or increase $\geq 1.5$ to $1.9$ reference SCr</td>
<td>$&lt; 0.5$ ml/kg/hr for $&gt; 6$ consecutive hours</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Increase $\geq 2$ to $2.9$ x reference SCr</td>
<td>$&lt; 0.5$ ml/kg/hr for $&gt; 12$ hours</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Increase $\geq 3$ x reference SCr or increase $\geq 354\mu$mol/L or commenced on renal replacement therapy (RRT) irrespective of stage</td>
<td>$&lt; 0.3$ ml/kg/hr for $&gt; 24$ hours or anuria for $12$ hours</td>
</tr>
</tbody>
</table>
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 an 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) \(\text{C}_6\text{H}_7\text{O}_7\)
  - 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.
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
- Effluent
- Dialysate Fluid
- Substitute Fluid
- Filter
- Calcium
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)
Clogging versus Clotting

Membrane in normal operation

![Blood flow through normal membrane](image)

Clogged membrane (obstructed membrane)

![Blood flow through clogged membrane](image)

Clotted hollow fiber

![Blood flow through clotted hollow fiber](image)

The blood flows through 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

<table>
<thead>
<tr>
<th>Systemic iCa2+ (mmol/L)</th>
<th>&lt; 1.01</th>
<th>1.01 - 1.11</th>
<th>1.12 - 1.20</th>
<th>1.21 - 1.45</th>
<th>&gt; 1.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment with calcium Chloride</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Starting dose Calcium Chloride (mmol/L)</td>
<td>2.0</td>
<td>1.9</td>
<td>1.7</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Check first systemic iCa2+ and review calcium dose after</td>
<td>2 hours</td>
<td>6 hours</td>
<td>6 hours</td>
<td>6 hours</td>
<td>6 hours</td>
</tr>
</tbody>
</table>
Correcting and Maintaining Calcium Levels

Company protocol: checks repeated 6 hourly

<table>
<thead>
<tr>
<th>Systemic ionised calcium (mmol/l)</th>
<th>Change of calcium dose (calcium/filtrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.45</td>
<td>Reduction by 0.6 mmol/l and inform physician</td>
</tr>
<tr>
<td>1.31 – 1.45</td>
<td>Reduction by 0.4 mmol/l</td>
</tr>
<tr>
<td>1.21 – 1.30</td>
<td>Reduction by 0.2 mmol/l</td>
</tr>
<tr>
<td>1.12 – 1.20</td>
<td>No change</td>
</tr>
<tr>
<td>1.05 – 1.11</td>
<td>Rise by 0.2 mmol/l</td>
</tr>
<tr>
<td>0.95 – 1.04</td>
<td>Rise by 0.4 mmol/l</td>
</tr>
<tr>
<td>&lt; 0.95</td>
<td>Rise by 0.6 mmol/l and inform physician</td>
</tr>
</tbody>
</table>

Adapted Protocol

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

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)

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 vas cath

Huriaux et al  Anaest Crit care Pain Med 2017
Vascular Access Length

Preferential insertion site of RRT catheter and corresponding catheter length.

<table>
<thead>
<tr>
<th>Insertion location</th>
<th>Catheter length</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Right internal jugular</td>
<td>15 cm</td>
</tr>
<tr>
<td>2. Right or left femoral</td>
<td>25 cm</td>
</tr>
<tr>
<td>3. Left internal jugular</td>
<td>20 cm</td>
</tr>
<tr>
<td>4. Dominant limb sub-clavian</td>
<td>Right: 15–20 cm, left: 20 cm</td>
</tr>
<tr>
<td>5. Non-dominant limb sub-clavian</td>
<td>Right: 15–20 cm, left: 20 cm</td>
</tr>
</tbody>
</table>

Evidence recommends femoral or right internal jugular and avoiding left internal jugular or subclavian — KDIGO guidelines (2012)
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 1.8m²
- Blood volume 130mls
- Wall thickness/inner diameter 35/220μm
Filter type: AV100s versus EMIC 2

- Enhanced Middle Molecule Clearance – comparable to CVVH
- Substantially stable albumin levels
- Reliable citrate anticoagulation

- High efficacy with low blood flows
- multiFiltrate 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 thrombocytopenia (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

It is now recommended start rates of 25mls/kg/hr
What dose should you use

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

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

- 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

<table>
<thead>
<tr>
<th></th>
<th>CVVHD</th>
<th>CVVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td>Small molecules clearance</td>
<td>✫</td>
<td>✫</td>
</tr>
<tr>
<td>Large molecules clearance</td>
<td>✫ ✭</td>
<td>✫</td>
</tr>
<tr>
<td></td>
<td>(depends on membrane permeability)</td>
<td></td>
</tr>
<tr>
<td>Hemofilter Life</td>
<td>✫</td>
<td>✫</td>
</tr>
<tr>
<td>Citrate Load</td>
<td>✫</td>
<td>✗</td>
</tr>
<tr>
<td>Low Q_b</td>
<td></td>
<td>Clearance depends on Q_b</td>
</tr>
<tr>
<td>Nurses Workload</td>
<td>✫</td>
<td>✗</td>
</tr>
<tr>
<td>Costs</td>
<td>✫</td>
<td>✗</td>
</tr>
</tbody>
</table>
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 phosphate
• 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

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