Anticoagulation Workshop 2011: Citrate

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University of Alabama at Birmingham
CRRT San Diego 2011
Case presentation

- 48 YO F with history of alcoholic abuse is admitted with sepsis and multi-organ failure
- She is intubated and hypotensive
- Laboratory:
  
<table>
<thead>
<tr>
<th>136</th>
<th>95</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>9</td>
<td>4.0</td>
</tr>
</tbody>
</table>

  ABG: 7.22/20/69 on 100%
  WBC: 37K, Plt 80K, Hct 30%
  LFTs (mg/dL): TBili 2.2, AST 423, ALT 400
  INR 2.0, Lactate 6.0 mg/dL

- She is initiated on CRRT
Case presentation

Which anticoagulant do you choose?
A. None
B. Unfractionated heparin
C. Citrate
D. Argatroban
E. Prostacyclin
F. Other
Option A: No anticoagulation

- Patient is initiated on CRRT without heparin, and the filter clots x 3 in 24 hrs
- Out of 24hrs, the patient has received 8 hrs of CRRT with no improvement in acidosis.

Venkataraman et al, J Crit Care, 2002
Option B: Heparin

- After 24hrs the patient’s filter clots once, and the patient drops her Hct by 10%
- Melena is noted by the nursing staff
- You choose citrate
Table 2  Mode, dilution site, filter material and anticoagulation for CRRT; CVVH, Continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; CVVHD, continuous venovenous hemodialysis; CAVHD, continuous arteriovenous hemodialysis

<table>
<thead>
<tr>
<th>CRRT mode</th>
<th>531/1006 (52.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVHDF</td>
<td>342/1006 (34.0%)</td>
</tr>
<tr>
<td>CVVHD</td>
<td>132/1006 (13.1%)</td>
</tr>
<tr>
<td>CAVHD</td>
<td>1/1006 (0.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dilution site for replacement fluid</th>
<th>509/870 (58.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predilution</td>
<td>361/870 (41.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Filter material</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycrylonitrile</td>
<td>457/975 (46.9%)</td>
</tr>
<tr>
<td>Polysulfone</td>
<td>209/975 (21.4%)</td>
</tr>
<tr>
<td>Polyamide</td>
<td>164/975 (16.8%)</td>
</tr>
<tr>
<td>Cellulose triacetate</td>
<td>89/975 (9.1%)</td>
</tr>
<tr>
<td>Polymethyl-methacrylate</td>
<td>27/975 (2.8%)</td>
</tr>
<tr>
<td>Polymethylene-sulfone</td>
<td>14/975 (1.4%)</td>
</tr>
<tr>
<td>Cellulose diacetate</td>
<td>11/975 (1.1%)</td>
</tr>
<tr>
<td>Others a</td>
<td>4/975 (0.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>429/1000 (42.9%)</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>99/1000 (9.9%)</td>
</tr>
<tr>
<td>Nafamostat mesilate</td>
<td>61/1000 (6.1%)</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>44/1000 (4.4%)</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>11/1000 (1.1%)</td>
</tr>
<tr>
<td>Hirudin</td>
<td>9/1000 (0.9%)</td>
</tr>
<tr>
<td>Heparin-protamine</td>
<td>6/1000 (0.6%)</td>
</tr>
<tr>
<td>Others b</td>
<td>3/1000 (0.3%)</td>
</tr>
<tr>
<td>Combination c</td>
<td>7/1000 (0.7%)</td>
</tr>
<tr>
<td>No anticoagulation</td>
<td>331/1000 (33.1%)</td>
</tr>
</tbody>
</table>

a 3 Polyester-polymer-alloy, 1 ethylene-vinyl alcohol; b 2 danaparoid, 1 warfarin; c 4 heparin-citrate, 2 heparin-prostacyclin, 1 nafamostat mesilate-low-molecular-weight heparin
<table>
<thead>
<tr>
<th></th>
<th>Design</th>
<th>Citrate</th>
<th>Heparin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monchi 2004</td>
<td>R cross-over N=20</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Kutsogiannis 2005</td>
<td>RCT N=30</td>
<td>RR 0.17 (0.03-1.04)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Betjes 2007</td>
<td>RCT N=48</td>
<td>0%</td>
<td>33%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oudemans 2009</td>
<td>RCT N=200</td>
<td>6%</td>
<td>16%</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Citrate and transfusion: RCT’s

<table>
<thead>
<tr>
<th>Design</th>
<th>Citrate</th>
<th>Heparin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monchi 2004</td>
<td>R cross-over N=30</td>
<td>0.2 0-2.0</td>
<td>1.0 0-4.0</td>
</tr>
<tr>
<td>Betjes 2007</td>
<td>RCT N=48</td>
<td>0.43</td>
<td>0.88</td>
</tr>
<tr>
<td>Oudemans 2009</td>
<td>RCT N=200</td>
<td>0.27 0-0.63</td>
<td>0.36 0-0.83</td>
</tr>
</tbody>
</table>
Why citrate? RCTs

- Regional anticoagulation
- No additional bleeding risk
- Longer hemofilter life

Largest Citrate RCT

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Citrate n=97</th>
<th>Nadroparin n=103</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>73 (64-79)</td>
<td>73 (67-79)</td>
</tr>
<tr>
<td>med-CS-Surg(%)</td>
<td>44-32-24</td>
<td>46-31-23</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>APACHE II</td>
<td>28 (7.9)</td>
<td>28 (6.9)</td>
</tr>
<tr>
<td>SOFA</td>
<td>11 (10-13)</td>
<td>11 (10-14)</td>
</tr>
<tr>
<td>RIFLE start HF</td>
<td>3 (2-3)</td>
<td>3 (2-3)</td>
</tr>
<tr>
<td>Time to start (d)</td>
<td>1.9(0.24-3.2)</td>
<td>1.8(0.28-3.4)</td>
</tr>
<tr>
<td>UF flow (ml/kg/min)</td>
<td>36 ± 17</td>
<td>33 ± 13</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th></th>
<th>Citrate (n = 97)</th>
<th>Nadroparin (n = 103)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events needing discontinuation of study anticoagulant, %</td>
<td>2</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding, %</td>
<td>6</td>
<td>16</td>
<td>0.08</td>
</tr>
<tr>
<td>Circuit survival time (all reasons), h</td>
<td>27 (13-47)</td>
<td>26 (15-43)</td>
<td>0.68</td>
</tr>
<tr>
<td>Renal recovery (all patients), %</td>
<td>69</td>
<td>52</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal recovery (surviving patients), %</td>
<td>97</td>
<td>86</td>
<td>0.08</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>41 (21-51)</td>
<td>57 (48-62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Three-month mortality, %</td>
<td>45 (35-55)</td>
<td>62 (53-72)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Oudemans-van Straaten et al. Crit Care Med 2009

- Post-dilutional CVVH
- Blood flow 220 ml/min
- Citrate 3 mmol/L blood flow
Mortality Results

Oudemans-van Straaten et al. Crit Care Med 2009
RCA vs. systemic UFH with CVVH: RCT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HF-Citrate</th>
<th>HF-Bicarbonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Gender (n, male)</td>
<td>57 (65.5%)</td>
<td>59 (71.1%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.72 (15.29)</td>
<td>65.11 (12.46)</td>
</tr>
<tr>
<td>Ethnic group (n, Caucasian)</td>
<td>85 (97.7%)</td>
<td>81 (97.6%)</td>
</tr>
<tr>
<td>Sepsis (n)</td>
<td>67 (77%)</td>
<td>61 (73.5%)</td>
</tr>
<tr>
<td>Post-operative (n)</td>
<td>41 (47.1%)</td>
<td>41 (49.4%)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>9.95 (2.95)</td>
<td>9.55 (2.59)</td>
</tr>
<tr>
<td>APACHE II score (Glasgow Coma Scale excluded)</td>
<td>21.83 (5.07)</td>
<td>22.04 (5.51)</td>
</tr>
</tbody>
</table>

- Hemofilter patency was significantly longer in the HF-Citrate group compared with the HF-Bicarbonate group (37.5 ± 23 h vs. 26.1 ± 19 h, P < 0.001, n = 87/81)

- More patients in the HF Bicarbonate group (14.5%) had bleeding episodes under CVVH than patients in the HF-Citrate group (5.7%)

- Mean occurrence of bleeding per CVVH day was 0.03 ± 0.13 in the HF-Citrate group and 0.05 ± 0.18 in the HF-Bicarbonate group (n = 87/81, P = 0.06)

Citrate anticoagulation

Intrinsic pathway
- XII → XIIa
- XI → Xla
- IX → IXa

Extrinsic pathway
- VII → VIIa
- V
- Prothrombin
- Ca++
- Tissue factor
- Ca++
- Coagulant active phospholipid (e.g. platelet membrane)
- X
- Xa
- Thrombin
- Fibrinogen
- Fibrin
- XIIIa
- Cross linked fibrin
Citrate anticoagulation

- Chelates free Ca$^{+2}$ in extracorporeal circuit
- Prevents activation of Ca$^{+2}$-dependent procoagulants
- Anticoagulant effect measured by iCa$^{+2}$
- Anticoagulation reversed by Ca$^{+2}$ infusion

Citrate + iCa $\rightarrow$ Calcium citrate

Biologically inactive measurable as total Ca
Citrate

- Normal blood levels of citrate: 0.05 mmol/L
- Bleeding time $\rightarrow \infty$ at citrate levels of 4 to 6 mmol/L ($iCa^{2+} < 0.25$ mmol/L)
- Levels of 12 to 15 mmol/L required for stored blood products for transfusion therapy
Calcium plasma distribution

Complexed calcium (~10%) (salts, calcium phosphate)
~ 0.05 mmol/L

Protein-bound calcium (~40%) (albumin)
~ 0.95 – 1.2 mmol/L

Ionized calcium (~50%)
~ 1.1 – 1.3 mmol/L

Total calcium
~ 2.2 - 2.6 mmol/L
Citrate metabolism

- Citric acid has plasma half life of 5 mins
- Rapidly metabolized by liver, kidney and muscle cells

\[
\text{Na}_3\text{Citrate} + 3\text{H}_2\text{CO}_3 \leftrightarrow \text{Citric Acid} + 3\text{NaHCO}_3
\]

\[
3\text{H}_2\text{CO}_3 + \text{H}_2\text{O} + 3\text{NaHCO}_3 \rightarrow 4\text{H}_2\text{O} + 6\text{CO}_2
\]

Clearance of citrate

- Extracorporeal clearance
  - Clearance same as urea
  - Sieving coefficient 0.87-1.0
  - CVVH = CVVHD clearance
  - Depends on citrate concentration in the filter and filtration fraction

Citrate

- **Advantages**
  - Regional, avoids bleeding complications
  - Doubles as buffer
  - Highly effective in studies (> heparin)
  - No thrombocytopenia

- **Disadvantages**
  - Metabolic complications
  - Complex protocols
Metabolic consequences

- Metabolic alkalosis
  - Citrate overdose/toxicity

- Metabolic acidosis
  - Citrate toxicity in setting of severe liver disease or hypoperfusion

- Hypernatremia
  - Hyperosmolar citrate solutions

- Hypocalcemia and hypercalcemia
  - Inappropriate calcium supplementation
Citrate toxicity

- Risk Factors
  - Liver Disease
  - Nursing or pharmacy errors: overdose
  - Shock liver; severe hypoperfusion states
- Detection
  - Rising anion gap, worsening metabolic acidosis
  - Falling systemic iCa$^{2+}$
  - Escalating Ca$^{2+}$ infusion requirements
  - Total Ca$^{2+}$ : Systemic iCa$^{2+}$ Ratio > 2.5:1 (increased Ca$^{2+}$ gap)

$$\text{Calcium Ratio} = \frac{\text{Total Ca}^{2+} (mg/ dL) \cdot 0.25}{\text{Systemic ion Ca}^{2+} (mmol/L)}$$

Patients with cirrhosis

Citrate pharmacokinetics and metabolism in cirrhotic and noncirrhotic critically ill patients

Ludwig Kramer; Edith Bauer; Christian Joukhadar; Wolfram Strobl; Alexandra Gondo; Christian Madl; Alfred Gangl

Crit Care Med 2003

Table 3. Citrate pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Cirrhotic Patients</th>
<th>Control Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose, mmol</td>
<td>77 ± 21</td>
<td>72 ± 10</td>
<td>.40</td>
</tr>
<tr>
<td>(C_{\text{baseline}}), mmol/L</td>
<td>0.51 ± 0.13</td>
<td>0.06 ± 0.13</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(C_{\text{max}}), mmol/L</td>
<td>1.68 ± 0.50</td>
<td>1.01 ± 0.29</td>
<td>.007</td>
</tr>
<tr>
<td>(t_{\text{max}}), mins</td>
<td>115 ± 12</td>
<td>114 ± 16</td>
<td>.95</td>
</tr>
<tr>
<td>AUC, mmol \times \text{min/L}</td>
<td>282 ± 130</td>
<td>131 ± 68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(t_{1/2}), mins</td>
<td>69 ± 33</td>
<td>36 ± 18</td>
<td>.001</td>
</tr>
<tr>
<td>(V_{d_{\text{app}}}})</td>
<td>27 ± 9</td>
<td>29 ± 10</td>
<td>.52</td>
</tr>
<tr>
<td>(V_{d_{\text{a}}})</td>
<td>23 ± 6</td>
<td>21 ± 6</td>
<td>.34</td>
</tr>
<tr>
<td>Clearance, mL/min</td>
<td>340 ± 185</td>
<td>710 ± 397</td>
<td>.002</td>
</tr>
</tbody>
</table>

\(C_{\text{baseline}}\), baseline concentration; \(C_{\text{max}}\), maximum concentration; \(t_{\text{max}}\), time to maximum concentration; AUC, area under the concentration time curve; \(t_{1/2}\), citrate half life; \(V_{d_{\text{app}}}}\), apparent volume of distribution; \(V_{d_{\text{a}}}\), volume of distribution at steady state.

Data are represented as mean ± so.

- Citrate clearance assessed in 32 (cirrhotic=16) critically ill patients
- Infusion of sodium citrate and calcium for 2hrs

NB: 17 patients (15 cirrhotics) with plasma citrate level > 1.5 mmol/L
Only 3 with Tot Ca/ionized Ca ratio > 2.5
Which citrate protocol?

- Citrate solutions
- Method of citrate delivery
- CRRT circuit options
# Commercial citrate solutions

<table>
<thead>
<tr>
<th>Components</th>
<th>4% Sodium Citrate</th>
<th>ACD A: 2.2% Sodium Citrate</th>
<th>ACD B: 1.32% Sodium Citrate</th>
<th>Prismocitrate (only available in Europe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (meq/L)</td>
<td>408</td>
<td>224</td>
<td>135</td>
<td>136</td>
</tr>
<tr>
<td>Sodium Citrate (mmol/L)</td>
<td>136</td>
<td>113</td>
<td>68</td>
<td>10</td>
</tr>
<tr>
<td>Citric Acid (g/L)</td>
<td></td>
<td>7.3</td>
<td>4.4</td>
<td>4.2</td>
</tr>
<tr>
<td>Dextrose (g/L)</td>
<td></td>
<td>24.5</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>Bag Size (mL)</td>
<td>250 &amp; 500</td>
<td>500 &amp; 1000</td>
<td>500</td>
<td>5000</td>
</tr>
</tbody>
</table>
Citrate delivery

- Fixed relationship between blood flow and citrate delivery

- Titration of citrate delivery based on iCa$^{2+}$
Citrate delivery: fixed

<table>
<thead>
<tr>
<th>QB (mL/min)</th>
<th>4% TSC (mL/hr)</th>
<th>ACD-A (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>175</td>
<td>210</td>
</tr>
<tr>
<td>125</td>
<td>218</td>
<td>262</td>
</tr>
<tr>
<td>150</td>
<td>262</td>
<td>315</td>
</tr>
<tr>
<td>200</td>
<td>350</td>
<td>420</td>
</tr>
</tbody>
</table>

Amount of citrate delivered to achieve blood citrate concentration of 4 mmol/L depends on blood flow

Calcium is infused through a separate central line to replace Ca$^{2+}$ lost in ultrafiltrate.

Citrate is metabolized primarily in liver to HCO$_3^-$, Bound Ca$^{2+}$ is released.

Citrate is titrated to normalize iCa$^{2+}$ and prevent systemic anticoagulation.

Post filter iCa$^{2+}$ is monitored and used to titrate citrate rate to assure anticoagulation.

Returning blood combines with venous blood in body, normalizing iCa$^{2+}$ and preventing systemic anticoagulation.
Circuit Options for CVVH

Post-dilution

Pre-dilution

Blood flow 120-200 ml/min
UF 1200-4000 ml/min
Citrate 15-40 mmol/L
MGH Citrate Protocol (CVVH)

**Prefilter Fluid: Isotonic Citrate**

- Na\(^+\) 145 mEq/L
- Cl\(^-\) 106.5 mEq/L
- Citrate\(^3-\) 40 mEq/L (13.3 mmol/L)
- Mg\(^{2+}\) 1.5 mEq/L
- Dextrose 0.2%

**Rate:** 1600 mL/hr
21.3 mmol/h citrate

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**Baxter BM25 with Renaflo II HF 700**

- \(Q_E = Q_R + Q_{FR}\)
- \(Q_B = 93.3\) mL/min (120 mL/min including prefilter rate)

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**Patient**

- iCa\(^{2+}\) 1.0-1.1 mmol/L

---

**Ca\(^{2+}\) Gluconate**

- 93 mEq/L (20 g/L) in D5W
- **Rate:** 50-70 mL/hr

---

Gainesville Protocol (CVVH)

Prefilter Fluid: PrismaSate BGK 2/0
- Na⁺ 140 mEq/L
- Mg²⁺ 1 mEq/L
- K⁺ 2 mEq/L
- Cl⁻ 108 mEq/L
- HCO₃⁻ 32 mEq/L
- Lactate 3 mEq/L
- Dextrose 110 mg/dL

Rate: 3000 mL/hr

Filter patency:
- 24 hrs- ~55%
- 48 hrs- ~40%
- 72 hrs- ~20%

ACD-A Citrate®
- Rate: 225 mL/hr
- 25.5 mmol/hr citrate

\[ Q_E = Q_R + Q_{FR} \]

Munjal and Ejaz. Nephrology 2006; 11: 405-409
Circuit Options for CVVHD

Blood flow 50-200 ml/min
Dialysate flow 1000-2000 ml/hr
Citrate 17.5-35 mmol/hr
UAB Citrate Protocol (CVVHHD)

**Prefilter Fluid:** 3L bag
- 2% Trisodium Citrate
  - Citrate\(^{3-}\) 204 mEq/L
  - Na\(^+\) 204 mEq/L
  - Dextrose 2.5%

**Rate:** 250 mL/hr
- 17.5 mmol/h citrate

**Dialysate:** 3L bag
- Na\(^+\) 140 mEq/L
- Cl\(^-\) 143 mEq/L
- K\(^+\) 3 mEq/L
- MgSO\(_4\) 1 mmol/L

**Rate:** 1000 mL/hr

**Gambro Prisma with M60 AN69 Filter**

\[ Q_E = Q_R + Q_{FR} + Q_D \]

**Prefilter Fluid**
Circuit Options for CVVHDF
San Diego Protocol (CVVHDF)

**Dialysate:** 4L bag
- **Na**⁺ 117 mEq/L
- **K**⁺ 4 mEq/L
- **MgSO₄** 1 mmol/L
- **HCO₃⁻** 0-40 mEq/L
- **Cl**⁻ 81-121 mEq/L
- Dextrose 0.1%

**Rate:** 1000 mL/hr

**Predilution Fluid:** 0.9% NS
- **Rate:** 500 mL/hr

**4% Na₃Citrate, 2L bag**
- **Rate:** 140-220 mL/hr
  - 19-29 mmol/hr citrate

**Postfilter Fluid:** 0.9% NS
- **Rate:** 200-1000 mL/hr

**Patient**
- **iCa²⁺** 1.12-1.32 mmol/L

**CaCl₂**
- 133 mEq/L
- **Rate:** 40-80 mL/hr

**Qₑ = Qₑ_R₁ + Qₑ_FR + Qₑ_D**

Sunnybrook Protocol (CVVHDF)

**ACD-A Citrate® (Baxter)**
- Na$_3$Citrate: 74.8 mmol/L
- Citric Acid: 38 mmol/L
- Dextrose: 123.6 mmol/L

**Rate:** 150 mL/hr
- 17 mmol/hr citrate+citric acid

**Prefilter Fluid: NS 0.9%**
- Started for HCO$_3^-$ > 25
- **Rate:** 0-1000 mL/hr

**Gambro Prisma with M100 AN69 Filter**

**Dialysate: 3.24 L bag**
**Normocarb® (DSI)**
- Na$^+$: 140 mEq/L
- Cl$: 106.5$ mEq/L
- HCO$_3^-$: 35 mEq/L
- Mg$^{2+}$: 1.5 mEq/L

**Rate:** 1000-2000 mL/hr

**PF iCa$^{2+}$ (0.25-0.35 mmol/L)**

**CaCl$_2$**
- 72 mEq/L in D5W
- **Rate:** 50 mL/hr

**Patient**
- iCa$^{2+}$
- 0.9-1.2 mmol/L

**Filter patency:**
- 24 hrs-94%
- 48 hrs-90%
- 72 hrs-72%

*Tobe SW et al. J Crit Care 2003*
Dialysate PrismaSate
B25GK4/0: 5 L bag
Na⁺ 140 mmol/L
Cl⁻ 120.5 mmol/L
HCO₃⁻ 22 mmol/L / lactate 3 mmol/L
K⁺ 4.0 mmol/L
Mg 0.75 mmol/L
Gluc 110 mg/dL
Rate: 1000-2500 mL/hr

Prefilter Fluid: 4 L bag
0.5% Trisodium Citrate
Citrate³⁻ 18 mmol/L
Na⁺ 140 mmol/L
Rate: 1000-2000 mL/hr

Gambro Prisma Pre-Pump Pre-Dilution Set

Gambro Prisma with M100 AN69 Filter

Qₚₐｔ ℎ  =  Qₐᵢₙ₊ₑ - Qₐᵢₙ₋ᵣ

Filter patency:
24 hrs-89%
48 hrs-82%
72 hrs-80%

Patient

Ca²⁺ Gluconate
38.75 mmol/L
Initial Rate: 60 mL/hr

Tolwani et al. CJASN 2006
Monitoring

- Circuit serum ionized calcium q 6-8^H
  - keep 0.25-0.35 mmol/l
- Systemic serum ionized calcium q 6-8^H
  - keep 0.90-1.0 mmol/l
- Serum Total Ca, PO_4 and Mg q 12 -24^H
Case presentation continued…

Which citrate formulation do you use? At what rate for a blood flow of 200 ml/min?

1. 4.0% TSC: 350 ml/hr
2. 2.2% ACD A: 420 ml/hr
3. 1.32% ACD B: 800 ml/hr

How often do nurses have to change the bags??????

What labs do you check? How often?

Post filter iCa, Total Ca, Chem 7
Check labs initially q 6 hrs
You decide to use 2.2% ACD-A. 

Where would you deliver the citrate? 

A. Pre-filter replacement fluid 
B. Via stopcock at access site
The patient continues on CVVHDF for 48 hrs

- CRRT Parameters:
  - BF 100 ml/min
  - RF 1600 ml/hr
  - D 1600 ml/hr
  - FR 300 ml/hr
  - ACD-A 200 ml/hr

- CRRT Labs:
  - Post Filter iCa: 0.25 mmol/L
  - Systemic iCa: 0.9 mmol/L
  - Serum Total Ca: 8.2 mg/dl
  - Calcium gtts is at 80 ml/hr
Case continued…

- Shift change occurs & the new nurse calls you with a syst iCa 0.67 mmol/L

- **What do you do?**
  - Ask from where the iCa level has been drawn
  - Ask where the calcium is being infused
  - Ask where the citrate is being delivered
Stat labs:

- 2 hrs later…
  - Pt’s BP drops & requires escalation of norepinephrine
  - Telemetry reveals prolonged QTc interval
  - Stat labs are sent

- Stat Labs:
  - Systemic total Ca 10.8 mg/dl
  - Systemic iCa 0.70 mmol/L
  - Serum bicarbonate 37 mEq/L
  - Serum Na 154 mEq/L

- What has happened to the patient?
Citrate toxicity

- **Stat labs:**
  - Systemic total Ca 10.8 mg/dl
  - Systemic iCa 0.70 mmol/L
  - Serum bicarbonate 37 mEq/L
  - Serum Na 154 mEq/L

- **What has happened to the patient?**
  - Citrate toxicity calculation =
  - Systemic Ca (mg/dl) $\times$ 0.25 / Systemic iCa
  - $10.9 \times 0.25 / 0.70 = 3.9$
  - If the ratio > 2.5, then the patient is citrate toxic
Citrate toxicity

The Patient’s citrate toxicity was the result of the nurse hanging citrate (ACD-A) at the stopcock position and in the dialysate position. The patient was receiving 1800 ml of citrate an hour!

**Bonus Question:**

Finally, How would you correct this catastrophe?
Case 2

- 48 yo M with hepatitis B cirrhosis / EtOH abuse found “down”
- Vitals:
  - T 102.3° F, HR 112, BP 73/30, RR 47
- Labs:
  - WBC 32.5, Plt 39, Na 128, K 6.0, bicarbonate 14, BUN 82, Cr 3.6, anion gap 19, TBili 29, AST 3196, ALT 1774. Ca 6.7
- Diagnosis:
  - Septic shock and multilobar pneumonia
- He develops AKI and is started on CVVHDF
  - BF 130 mL/min
  - Pre-dilution RF 0.5% citrate 1500 mL/hr
  - Dialysate 1500 mL/hr
Case 2

- 6 hours later…
  - CaGlu infusion 60 mL/hr
  - Systemic iCa 0.69 mmol/L
  - Post-filter iCa < 0.25 mmol/L

- 12 hrs later…
  - CaGlu infusion 120 mL/hr
  - Systemic iCa 0.70 mmol/L
  - Total Ca 7.8 mg/dL
  - Bicarbonate 17 mEq/dL
  - Anion gap 28

What’s the problem?
Case 2: citrate toxicity

- Calcium Ratio
  - Total Ca 7.8 mg/dL
  - Systemic iCa 0.67 mmol/L
  - Ratio = 7.8 × 0.25 / 0.67 = 2.9.

- Patient is citrate toxic

- Management
  - Decrease citrate infusion rate
  - Decrease blood pump speed
  - Increase dialysate flow rate
  - Discontinue citrate
Sustained Low Efficiency Dialysis (SLED) and Citrate

- Published protocols
  - Morgera et al. Nephrol Clin Pract 2004
  - Finkel and Foringer. Ren Fail 2005

- Components
  - 4% TSC infused into arterial line
  - Post-filter iCa 1.0-1.4 mEq/L
  - QB 200 ml/min
  - QD 70-200 ml/min
  - No Ca dialysate with IV Ca replacement or
  - Low Ca (2 mEq/L) dialysate without IV Ca replacement