Anticoagulation Workshop 2012: Citrate

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University of Alabama at Birmingham
CRRT San Diego 2012
Case Presentation

- 48 YO F with history of alcoholic abuse is admitted with sepsis and multi-organ failure
- She is mechanically ventilated and hypotensive
- **Laboratory:**
  - 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
Why Citrate?
Citrate and Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>citrate Events</th>
<th>Total</th>
<th>control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betjes MG 2007</td>
<td>0</td>
<td>21</td>
<td>10</td>
<td>27</td>
<td>19.6%</td>
<td>0.06 [0.00, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Fealy N 2007</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Hetzel GR 2011</td>
<td>5</td>
<td>87</td>
<td>12</td>
<td>83</td>
<td>26.0%</td>
<td>0.40 [0.15, 1.08]</td>
<td></td>
</tr>
<tr>
<td>Kutsogiannis DJ 2005</td>
<td>1</td>
<td>16</td>
<td>8</td>
<td>14</td>
<td>18.1%</td>
<td>0.11 [0.02, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Monchi M 2004</td>
<td>0</td>
<td>26</td>
<td>1</td>
<td>23</td>
<td>3.4%</td>
<td>0.30 [0.01, 6.94]</td>
<td></td>
</tr>
<tr>
<td>Oudemans-van Straaten HM 2009</td>
<td>6</td>
<td>97</td>
<td>16</td>
<td>103</td>
<td>32.9%</td>
<td>0.40 [0.16, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>257</td>
<td>260</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.28 [0.15, 0.50]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 12

Heterogeneity: Chi² = 3.16, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.27 (P < 0.0001)

### Why Citrate?

*Citrate and Circuit Patency*

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>citrate</th>
<th>control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Beljes MG 2007</td>
<td>39</td>
<td>15.7</td>
<td>70</td>
<td>42.3</td>
</tr>
<tr>
<td>Fealy N 2007</td>
<td>16.3</td>
<td>2.4</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Hetzel GR 2011</td>
<td>37.5</td>
<td>23</td>
<td>87</td>
<td>26.1</td>
</tr>
<tr>
<td>Kutsogiannis DJ 2005</td>
<td>125.5</td>
<td>16.8</td>
<td>36</td>
<td>40.9</td>
</tr>
<tr>
<td>Monchi M 2004</td>
<td>81.4</td>
<td>27</td>
<td>26</td>
<td>36.1</td>
</tr>
<tr>
<td>Oudemans-van Straaten HM 2009</td>
<td>28.5</td>
<td>8.8</td>
<td>97</td>
<td>27.5</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>326</td>
<td></td>
<td>332</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\tau^2 = 785.58$; $\chi^2 = 696.77$, df = 5 ($P < 0.00001$); $I^2 = 99$

Test for overall effect: $Z = 2.00$ ($P = 0.05$)
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>

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

**Results**

<table>
<thead>
<tr>
<th>Adverse events needing discontinuation of study anticoagulant, %</th>
<th>2</th>
<th>19</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<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
Mortality Results

Per protocol patients

Cum Survival

Survival time (days)

P = 0.02

Oudemans-van Straaten et al. Crit Care Med 2009
Citrate Anticoagulation

Intrinsic pathway
- XII
- XI
- IX

Extrinsic pathway
- X
- Ca++
- Tissue factor

Coagulant active phospholipid (e.g. platelet membrane)

Prothrombin

Thrombin

Fibrinogen

Fibrin

Cross linked fibrin

Ca++
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
Which of the following is indicative of adequate anticoagulation of citrate for CRRT?

A. CRRT circuit ionized calcium level of 0.25 mmol/L
B. Systemic ionized calcium level of 0.7 mmol/L
C. Serum citrate level of 1 mmol/L
D. Total calcium level of 2.2 mmol/L
Citrate

- Normal blood levels of citrate: 0.05 mmol/L

- Bleeding time $\rightarrow \infty$ at citrate levels of 4 to 6 mmol/L ($i\text{Ca}^{2+} < 0.25$ mmol/L)

- Levels of 12 to 15 mmol/L required for stored blood products for transfusion therapy
Calcium Plasma Distribution

Total calcium (~2.2 - 2.6 mmol/L)

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
Citrate Metabolism

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

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

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)

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

Calcium Gap

- **Total calcium**
  - Ionized calcium
  - Protein bound calcium
  - Complexed calcium
- **Calcium citrate**

- **mmol/L**: 3
- **mg/dL**: 12
  - 8
  - 4
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 $i\text{Ca}^{2+}$
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 chelates free ionized Ca\(^{2+}\).

Returning blood combines with venous blood in body, normalizing iCa\(^{2+}\) and preventing systemic anticoagulation.

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

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

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

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

**Baxter BM25 with Renaflo II HF 700**

**Ca\(^{2+}\) Gluconate**
- 93 mEq/L (20 g/L) in D5W
- **Rate:** 50-70 mL/hr

**PF iCa\(^{2+}\) (not monitored)**

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

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

**DIAPACT with F160**

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

**Patient**
- iCa²⁺: 1.19-1.32 mmol/L

**CaCl₂**

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 (CVVHD)

**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 Pre-Pump Pre-Dilution Set

\[ Q_R \]

\[ Q_D \]

**PF iCa\(^{2+}\) (0.25-0.5 mmol/L)**

**Q\(_B\)**
100-150 mL/min
(actual \(Q_B = Q_{B, \text{machine}} - Q_R\))

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

**Ca\(^{2+}\) Gluconate**
- 93 mEq/L (20 g/L) in D5W or H\(_2\)O

**Rate:** 60 mL/hr

**Tolwani AJ et al, KI, 2001, 60: 370-374.**
Circuit Options for CVVHDF

RF + Citrate

Citrate

RF

Q_B

Q_R

Q_D

V

Ca

V
San Diego Protocol (CVVHDF)

Dialysate: 4L bag
- $\text{Na}^+ \quad 117 \text{ mEq/L}$
- $\text{K}^+ \quad 4 \text{ mEq/L}$
- $\text{MgSO}_4 \quad 1 \text{ mmol/L}$
- $\text{HCO}_3^- \quad 0-40 \text{ mEq/L}$
- $\text{Cl}^- \quad 81-121 \text{ mEq/L}$
- Dextrose 0.1%

Rate: 1000 mL/hr

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

Gambro Prisma, Braun Diapact, or Hospal BSM 22

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

$\text{Q}_D$

$\text{Q}_R1$

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

Gambro Prisma, Braun Diapact, or Hospal BSM 22

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

$\text{Q}_D$

$\text{Q}_R1$

4% $\text{Na}_3\text{Citrate, 2L bag}$
- Rate: 140-220 mL/hr
  - 19-29 mmol/hr citrate

$\text{Q}_E = \text{Q}_R1 + \text{Q}_{\text{FR}} + \text{Q}_D$

$\text{Q}_R2$

Patient
- $\text{CaCl}_2$
  - $133 \text{ mEq/L}$
- Rate: 40-80 mL/hr
  - $\text{iCa}^{2+} \quad 1.12-1.32 \text{ mmol/L}$

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

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

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

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

Gambro Prisma with M100 AN69 Filter

Q$_E$ = Q$_R$ + Q$_{FR}$ + Q$_D$

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

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

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

Tobe SW et al. J Crit Care 2003
UAB Protocol (CVVHDF)

**Prefilter Fluid:** 4 L bag
- 0.5% Trisodium Citrate
  - Citrate\(^{3-}\) 18 mmol/L
  - Na\(^{+}\) 140 mmol/L
- Rate: 1000-2000 mL/hr

**Dialysate PrismaSate B25GK4/0:**
- 5 L bag
- Na\(^{+}\) 140 mmol/L
- Cl\(^{-}\) 120.5 mmol/L
- HCO\(_{3}\) 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

**Gambro Prisma with M100 AN69 Filter**

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

**Ca\(^{2+}\) Gluconate**
- 38.75 mmol/L
- Initial Rate: 60 mL/hr

**Tolwani et al. CJASN 2006**
Monitoring

- Circuit serum ionized calcium q 6-8\textsuperscript{H}  
  \[\text{keep 0.25-0.35 mmol/l}\]
- Systemic serum ionized calcium q 6-8\textsuperscript{H}  
  \[\text{keep 0.90-1.0 mmol/l}\]
- Serum Total Ca, PO\textsubscript{4} and Mg q 12 -24\textsuperscript{H}
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

What labs do you check? How often?

- Post filter iCa, Total Ca, Chem 7
- Check labs initially q 6 hrs

How often do nurses have to change the bags???????
Case Presentation Continued…

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) X 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?
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