Technical aspects of RRT in AKI: access, anticoagulation, drug dosage and nutrition

Marlies Ostermann
Chapter 3: Nutrition

Chapter 5.3: Anticoagulation

Chapter 5.4: Vascular access for RRT in AKI
Vascular access
5.4.1: We suggest initiating RRT in patients with AKI via an uncuffed nontunneled dialysis catheter, rather than a tunneled catheter. (2D)

5.4.2: When choosing a vein for insertion of a dialysis catheter in patients with AKI, consider these preferences (Not Graded):

1\textsuperscript{st} choice: right jugular vein
2\textsuperscript{nd} choice: femoral vein
3\textsuperscript{rd} choice: left jugular vein
Last choice: subclavian vein

Individual patient characteristics may require deviations from this order of preferences.
5.4.5: We suggest not using topical antibiotics over the skin insertion site of a nontunneled dialysis catheter in ICU patients with AKI requiring RRT. (2C)

5.4.6: We suggest not using antibiotic locks for prevention of catheter-related infections of nontunneled dialysis catheters in AKI requiring RRT. (2C)

No comment about duration / line changes
Anticoagulation
Anticoagulation

Hollow fibres providing surface area 0.8 – 2.1 m²
Filter clotting

Blood

ultrafiltrate

Hkt
1. Haemoconcentration

2. Thrombogenic circuit surface
   (coating of surface with plasma proteins → platelet aggregation)

3. Exposure of blood to air (ie. in drip chamber)

4. Risk factors:
   - low blood flow
   - high Hkt
   - hypercoagulable states
   - filters with large surface area
   - imperfect priming of filter
   - frequent interruption of blood flow
   - lipid infusions (incl propofol)
Inner surface of dialyzer membrane during hemodialysis therapy:

dense fibrin network with large amounts of aggregated erythrocytes despite heparin

Hofbauer R et al, KI 1999;56,1578–1583
Anticoagulation

- Heparin
- Prostacyclin
- No anticoagulation / regular saline flushes
- Regional anticoagulation:
  - with citrate
  - with heparin / protamine
1. No anticoagulation

flushes with 50-100 mls NaCl 0.9% into prefilter port every 15-30 mins
Prevention of circuit clotting without heparin

Saline flushes at regular intervals

Blood

\[\text{ultrafiltrate}\]
Prevention of circuit clotting without heparin

1. No anticoagulation

flushes with 50-100 mls NaCl 0.9% into prefilter port

Problems:
nursing workload
need to incorporate boluses into fluid balance

Additional tricks:
  increase blood flow rate
  change from post-dilution to pre-dilution (but↑ costs)
Haemofiltration

- Anticoagulation
- Postdilution replacement fluid
- Ultrafiltrate
- To patient
- Air detector
Haemofiltration

Predilution replacement fluid

Postdilution replacement fluid

ultrafiltrate

to patient

Air detector

anticoagulation
2. Prostacyclin

inhibitor of platelet aggregation
weaker anticoagulant than heparin
vasodilation
expensive
3. Regional anticoagulation

Heparin / Protamine combination

Complex
risk of rebound anticoagulation
side effects of protamine
3. Regional anticoagulation

Citrate / Calcium
Sodium citrate
Citrate Anticoagulation

Sodium citrate
Citrate Anticoagulation
Citrate Anticoagulation

Ionized Ca < 0.5 mmol/L  →  clotting cascade impaired
Ionized Ca < 0.3 mmol/L  →  clotting cascade completely inhibited
Citrate Anticoagulation

from patient

Air detector

Target: post filter Cai 0.25 – 0.35mmol/L

to patient

Citrate
Citrate Anticoagulation

Target: post filter Cai 0.25 – 0.35mmol/L
Citrate Anticoagulation

Less bleeding AND prolonged filter life

Gabutti et al.
Intensive Care Med 2002

Morgera et al.
Nephron Clin Pract 2004
Elimination of citrate:

- ~40-50% cleared across the filter
- ~50-60% eliminated via Krebs cycle in liver and skeletal muscle (and renal cortex)
Heparin: pro-inflammatory effects increases risk of bleeding

Citrate: no pro-inflammatory effects provides energy to mitochondria
Disadvantages of citrate anticoagulation

1. Metabolic derangements
   - metabolic alkalosis
   - hypocalcaemia
   - metabolic acidosis (citrate accumulation in liver failure)
   - hypomagnesaemia (citrate binds to Mg)
   - hypernatraemia

2. Reduced citrate metabolism in severe liver disease

3. Intolerance in “shock”
   i) oxygen is essential in Krebs cycle
   ii) patients with intracellular hypoxia and lactic acidosis cannot metabolise citrate → worsening acidosis declining serum Ca

4. Technical complexity

5. More expensive than heparin but safe / potentially cost effective
Chapter 5.2, page 98

“A major contra-indication for the use of citrate anticoagulation is severely impaired liver function or shock with muscle hypoperfusion, both representing a risk of citrate accumulation.”
Anticoagulation

Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study

Critical Care 2012, 16:R162

Observational study 2009 – 2011
28 ICU patients (ie. 43 CVVHD sessions) with decompensated CLD or ALF

Results:
- Circuit patency >72h in 74% of CVVHD sessions.
- Up to 29-fold elevated serum citrate levels at 72h
- PT ≤26% and serum lactate ≥3.4 mmol/L associated with citrate accumulation.
- Citrate stopped because of high CaT/Cai ratio in 3 patients

Conclusion: CVVHD using citrate for regional anticoagulation in liver failure patients is feasible.
Drug dosage
Principles of drug removal

**Drug factors:**
- Protein binding
- Hydrophilic vs lipophilic
- Volume of distribution
- Method of total body clearance

**Molecular size doesn’t matter much**
Most drugs < 1000 D
Membrane cut - off: 20 000 – 50 000 D
**Protein binding**

- Only drugs not bound to plasma proteins will be removed by CRRT
- Binding to Albumin, $\alpha_1$-acid glycoprotein, lipoprotein
- Drug-protein = 50,000 D

- Additional changes in ICU patients
  - pH
  - Albumin ↓
  - other drugs
Principles of drug removal

Drug dosing in continuous renal replacement therapy: general rules
Miet Schetz

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<table>
<thead>
<tr>
<th>Protein binding</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>High (~90%)</strong></td>
<td><strong>Midazolam</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Ceftriaxone</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Teicoplanin</strong></td>
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<tr>
<td></td>
<td><strong>Clindamycin</strong></td>
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<tr>
<td></td>
<td><strong>Amphotericin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Amiodarone</strong></td>
</tr>
<tr>
<td><strong>Low (&lt;15%)</strong></td>
<td><strong>Meropenem</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Gentamicin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Fluconazole</strong></td>
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<tr>
<td></td>
<td><strong>Metronidazole</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Aciclovir</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lisinopril</strong></td>
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</tbody>
</table>
Principles of drug removal

Volume of distribution

- Changes in critically ill patients
  - increased volume of distribution, esp in severe sepsis
  - altered protein binding

- only plasma level available for extracorporeal removal
  (vs interstitial or tissue concentrations)
Total Clearance
(ml/min)
= $C_{\text{I}_{\text{renal}}} + C_{\text{I}_{\text{non renal}}} ( + C_{\text{I}_{\text{filter}}})$

CRRT clearance important if $C_{\text{I}_{\text{renal}}} > 25\text{-}30\%$
Principles of drug removal

Renal clearance

High
- Benzylpenicillin (85%)
- Cefuroxime (96%)
- Ceftazidime (84%)
- Milrinone (80%)
- Digoxin (65%)
- Atenolol (94%)

Low (<25%)
- Erythromycin
- Clindamycin
- Amphotericin
- Cyclosporin
- Labetalol
- Hydralazine
<table>
<thead>
<tr>
<th>Drug</th>
<th>Vd (L/kg)</th>
<th>% renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>0.25</td>
<td>70%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.25</td>
<td>100%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.7</td>
<td>75%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.7</td>
<td>10%</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>0.7</td>
<td>75%</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>0.6</td>
<td>90%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1.5</td>
<td>100%</td>
</tr>
</tbody>
</table>

Is CRRT clearance important?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Protein Binding</th>
<th>Vd (L/kg)</th>
<th>CRRT Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylpenicillin</td>
<td>60%</td>
<td>0.3</td>
<td>✓</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>33%</td>
<td>0.19</td>
<td>✓</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>21%</td>
<td>0.23</td>
<td>✓</td>
</tr>
<tr>
<td>Digoxin</td>
<td>25%</td>
<td>5-8</td>
<td>✗</td>
</tr>
<tr>
<td>Milrinone</td>
<td>70%</td>
<td>0.3</td>
<td>?</td>
</tr>
<tr>
<td>Atenolol</td>
<td>&lt;5%</td>
<td>0.95</td>
<td>✓</td>
</tr>
</tbody>
</table>
Additional contributing factors

• Size of filter

• RRT dose

• Membrane interactions
  Adsorption of proteins on membrane
  Gibbs-Donan effect: retention of anionic drugs on protein of membrane

• Interruptions in RRT
Drug removal during CRRT

In practice:

Risk of under- and overdosing

Close relationship with ICU pharmacist
  altered pharmacokinetics of drugs
  dynamics of clinical condition

Regular review of drug chart
Defining Antibiotic Levels in Intensive care unit patients
International multi-centre study sponsored by ESICM grant

Point of prevalence study (Sept 2011)

Aim: to determine whether contemporary antibiotic dosing for critically ill patients is achieving concentrations associated with maximal antibacterial activity

Provisional results: Large variation!
Nutrition in RRT
Nutrition in RRT

Facts:
- Albumin is poor marker of nutrition in critically ill
- Protein hypercatabolism due to inflammation, stress, and acidosis is common in critically ill patients.
- Patients with AKI often already malnourished on admission to hospital (42%)
- Nutritional effects of CRRT:
  - loss of: glucose
  - aminoacids and small proteins
    (~10-15g amino acids/day ≈ 5-10g protein/day)
  - trace elements
  - water soluble vitamins (Vitamin B1, B6, C, folic acid)
ESPEN Guidelines on Enteral Nutrition: Adult Renal Failure

N. Cano, E. Fiaccadori, P. Tesinsky, G. Toigo, W. Druml,
DGEM: M. Kuhlmann, H. Mann, W.H. Hörl
## Summary of statements: Acute renal failure (ARF)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Recommendations</th>
<th>Grade&lt;sup&gt;71&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>General</td>
<td><strong>Macronutrient</strong> requirements are not so much determined by acute renal failure (ARF) as by the severity of the underlying disease, the type and intensity of extracorporeal renal replacement therapy, and by nutritional status and associated complications: <strong>Table 1</strong> Extracorporeal treatment induces increased losses of <strong>micronutrients</strong> which should be supplemented. Monitor micronutrient status because excessive supplementation may result in toxicity. In ICU patients with ARF, the <strong>electrolyte</strong> content of most 1500–2000 kcal enteral formulae is usually adequate. However, requirements can differ and have to be assessed individually. Plasma electrolyte monitoring should avoid hypokalaemia and/or hypophosphataemia after initiation of enteral nutrition (EN) (refeeding syndrome).</td>
<td></td>
</tr>
</tbody>
</table>
Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient:

Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.)

12. Patients receiving hemodialysis or continuous renal replacement therapy (CRRT) should receive increased protein, up to a maximum of 2.5 g/kg/d. Protein should not be restricted in patients with renal insufficiency as a means to avoid or delay initiation of dialysis therapy. (Grade: C)
KDIGO

3.3.5: We suggest providing nutrition preferentially via the enteral route in patients with AKI. (2C)

3.3.2: We suggest a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI. (2C)
3.3.3: We suggest to avoid restriction of protein intake with the aim of preventing or delaying initiation of RRT. (2D)

3.3.4: We suggest administering
- 0.8–1.0 g/kg/d of protein in noncatabolic AKI patients (2D)
- 1.0–1.5 g/kg/d in patients with AKI on RRT (2D)
- and up to 1.7g/kg/d in patients on CRRT and in hypercatabolic patients. (2D)

No comment about supplementation of vitamins or trace elements.
Conclusions

1. Access
   1\textsuperscript{st} choice: right jugular vein  \quad 2\textsuperscript{nd} choice: femoral vein
   3\textsuperscript{rd} choice: left jugular vein

2. Anticoagulation
   increasing popularity of citrate anticoagulation

3. Drug dosing
   complex
   still a lot of uncertainty
   DALI may provide new answers

4. Nutrition
   enteral nutrition
   ensure adequate protein intake
   lack of evidence for routine supplementation with vitamins and trace elements