Continuous Renal Replacement Therapy Overview

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Thanks to Humaira Nawer, PharmD for citrate slides!
In your institution, what is the preferred renal replacement therapy in your ICUs?

A. Intermittent hemodialysis
B. Continuous Renal Replacement Therapy
C. Slow Low Efficiency Dialysis
D. Something else….or I don’t know
Practice #3: Know what are nephrologists / intensivists are doing to your patient and their drug clearance.

**Renal Replacement Therapies (RRT)**

<table>
<thead>
<tr>
<th>Ambulatory/ESRD/Outpatient</th>
<th>Critically Ill/Acute Kidney Injury/Inpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peritoneal</strong></td>
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<td>CAPD</td>
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<td>CCPD</td>
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<td><strong>Intermittent</strong></td>
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<tr>
<td>IHD</td>
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<tr>
<td><strong>Prolonged Intermittent (PIRRT)</strong></td>
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<tr>
<td>SLED/-f</td>
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<tr>
<td>EDD</td>
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<td>SHIFT</td>
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<td><strong>Continuous (CRRT)</strong></td>
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<tr>
<td>CVVH</td>
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<tr>
<td>CVVHD</td>
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<tr>
<td>CVVHDF</td>
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ICU RRT Variability

• First RRT Choice for AKI in Malaysian ICUs

• **Modality:** CRRT 79%, IHD 16% PIRRT 5%

• **CRRT Type:** HF 72%, HDF 56%, HD 28%
  • Prescribed dose (mL/kg/h) : 30.6 (± 4.6)
  • Predilution 33%, Post 11%, Pre + Post 56%

• **PIRRT duration** 6.2 (± 1.8) hours
  • Blood flow 263.6 (± 67.4) mL/min
  • Dialysate Flow 294.4 (± 80.8) mL/min
What is CRRT?

- Continuous Renal Replacement Therapy
  - CVVH – Continuous venovenous hemofiltration
  - CVVHD - Continuous venovenous hemodialysis
  - CVVHDF - Continuous venovenous hemodiafiltration
- Renal replacement therapy for critically ill patients
  - 24 hrs/day, 7 days/wk
- Available in most US & Canadian ICUs
  - Common in Europe, Australia, New Zealand
Who gets CRRT?

- ICU patients too hemodynamically unstable to tolerate conventional hemodialysis
- Highly catabolic patients who might require hemodialysis 5-7 days/week
- Sepsis the most common co-morbidity
- Multisystem organ failure common
- Mortality rates ~50%
Diffusive Therapies: Dialysis (CVVHD)

• Commercial Dialysate is used
  • In 2018, you should not be making CRRT solutions!

• Good for small solute removal (<500 Da)
  • diffusion rate inversely proportional to MW
  • Less good for larger solutes (Vancomycin?)
Typical CVVHD orders

• Blood Flow – 150-200 mL/minute
• Dialysate Flow – 17-33 mL/min (1-2 L/hr)
• Net volume removal – 2 mL/min (120 mL/hr)
  • If patient getting net (5 mL/min) 300 mL/hr of meds & TPN
  • Suction turned up to remove 300 + 120 = 420 mL/hr
  • This 420 mL/hr (7 mL/min) is in addition to the dialysate flow coming out of dialyzer.

Blood in
150 mL/min

Drugs/TPN in
5 mL/min

Blood out
148 mL/min

40 mL/min
Effluent (Spent Dialysate) out

Dialysate in
33 mL/min
Convective Therapies: Hemofiltration (CVVH)

- No dialysate, removes plasma water as it seeps through membrane
- Removes small and large molecules easily
  - as long as they can fit through membrane
- Drug removal easy to calculate
  - based on sieving coefficient
  - ultrafiltrate concentration/plasma concentration
Typical CVVH orders

- Blood Flow – 150-200 mL/minute
- Ultrafiltrate Flow – 33 mL/min (1-2 L/hr)
- Net volume removal – 2 mL/min (120 mL/hr)
  - If patient getting 5 mL/min (300 mL/hr) of meds & TPN
  - UF replacement solution + TPN/Meds infused at to yield 2 mL/min fluid loss
How CVVH affects waste product removal - convectively

- Hematocrit going into hemofilter is 40%
- Coming out of filter is 45%
- Blood in has BUN concentration of 100 mg/dL
- UF out has BUN concentration of 100 mg/dL
- Blood coming out of hemofilter has BUN concentration of 100 mg/dL!
- How does patient’s BUN ever go down?
Coffee maker analogy for convective RRT
Combination therapies (CVVHDF)

- Most complicated because has convective and diffusive drug removal
- CVVHDF example when I want net 2 mL/min fluid loss in patient

**Diagram**
- Blood in: 150 mL/min
- Blood out: 148 mL/min
- Effluent out: 43 mL/min (2 + 5 + 16 + 20 mL/min)
- Dialysate in: 20 mL/min
- TPN/Meds + UF replacement: 5 + 16 mL/min
What CRRT Effluent Rate is Best?

- Most large trials show no difference in survival between higher vs. lower effluent rates
- KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines:
  - Aim to deliver an effluent volume of 20-25 mL/kg/h
Continuous Renal Replacement Therapy (CRRT)\textsuperscript{1,3}

Diagram adapted from: 
goo.gl/8p2fuQ
goo.gl/4x98j3
Anticoagulation for CRRT
CRRT Circuit Clotting\textsuperscript{2,5}

- Contact with tubing
- Turbulence
- No endothelium

Blood flows through CRRT circuit

Activation of platelets, inflammatory mediators, coagulation cascade

Fibrin deposition and clotting of the circuit/filter

Hofbauer et al. (1999)
Issues Associated with Clotting\textsuperscript{2,6}

- Reduced RRT treatment time and dose
- Increased expense, time, and workload
- Potential blood loss and increased transfusion needs
- Increased risk of infections
- Complicated drug pharmacokinetics

https://goo.gl/jqB6
Here are the CRRT anticoagulation options...

- No anticoagulation
- Saline flushes
- Heparin
- Regional heparinization
- Regional citrate
- Low-molecular weight heparin
- Thrombin inhibitors
- Nafamostat
- Prostacyclin
- Heparinoids
Here are the CRRT anticoagulation options...

- No anticoagulation
- Saline flushes
- Heparin
- Regional heparinization
- Regional citrate
- Low-molecular weight heparin
- Thrombin inhibitors
- Nafamostat
- Prostacyclin
- Heparinoids

https://goo.gl/WuhYpr
What anticoagulation do you use?
Citrate\textsuperscript{3,6,10}

- Not approved by the FDA for CRRT anticoagulation
- Approved as an anticoagulant for preparation of blood products
Citrate for Anticoagulation

Calcium citrate complex

35-50% removed by dialysis across hemofilter (depending on flow rates of blood, citrate)

Liver, kidney, skeletal muscle

Bicarbonate

https://goo.gl/TMB5Vw
https://goo.gl/3VK4b3
https://goo.gl/dJbjYN
https://goo.gl/fYQhNs
Patient

Pump

Calcium-containing replacement solution

Calcium-free dialysate

Effluent

Blood flow
150-300 mL/min

Diagram adapted from:
goo.gl/8p2fuQ
goo.gl/4x98j3
Citrate for Anticoagulation

General Protocol Considerations

- Citrate introduced at earliest point possible in the circuit before filter
- Replace calcium at the end of the extracorporeal circuit or through a separate line to replace calcium that is chelated and lost
- Must ensure that dialysis, citrate infusion, and calcium infusion are started and stopped simultaneously
Citrate for Anticoagulation

Adverse effects:

- Hypernatremia
- Metabolic alkalosis
- Hyperglycemia
- Hypocalcemia or hypercalcemia
- Hypomagnesemia
- Increased ion gap
Monitoring

- Electrolytes (Na, K, Cl, Ca, Mg)
  - Ionized calcium both in the circuit post-filter and in the patient → measure of anticoagulation
  - Total calcium to ionized calcium ratio (T/I)
- Blood sugar
- Blood gas
- Anion gap
- EKG

https://goo.gl/ccvYu7
Patient

Pump

Calcium-containing replacement solution

Calcium-free dialysate

Blood flow
150-300 mL/min

Diagram adapted from:
goo.gl/8p2fuQ
goo.gl/4x98j3
CRRT Drug Removal Mechanisms

• Adsorption to the membrane (usually ignored)
• Transmembrane drug clearance dependent on:
  • Small volume of distribution
  • Not protein bound – only free drug can cross CRRT membrane
• Drug molecular weight <2000 Daltons
  • Even “large” drugs (daptomycin, vancomycin, telavancin) will cross membrane
  • All CRRT membranes are “high-flux” dialyzers
Kinetics in ARF and RRT

Drug Dosing Recommendations Based on Sieving Coefficient (SC)

- CRRT Drug clearance a function of
  - Rate of effluent flow
  - Ability of drug to cross membrane (sieving coefficient)
- For drugs <2000 Daltons:
  - Sieving Coefficient ≈ % Free Fraction
  - Protein binding important determinant of CRRT clearance
CRRT Drug Removal

• CRRT Clearance = SC X Effluent Rate

• Mg lost/time =

• (Serum Concentration)(SC)(effluent rate)

• Vancomycin example:
  • SC = 0.8,
  • CRRT Effluent rate= 2L/hr
  • Vancomycin Serum Concentration = 20mg/L
  • Amount lost by CRRT=
    • 20 mg/L (0.8) (2L/hr) = 32 mg/hr

• Remember... Patient also lost drug via liver, residual renal clearance, etc.
Effects of CRRT Effluent Rates on Antibiotics

CRRT at 40 mL/min

CRRT at 20 mL/min

Log Antibiotic Concentration

Time (Hours)

MIC = 2

MIC = 1
Of last 10 CRRT patients at your institution…
How many of them perished from infection-related issues (sepsis, etc)?

- A 0-1 patient
- B 2-3 patients
- C 3-4 patients
- D 4 or more patients
Of last 10 CRRT patients at your institution…
How many experienced symptoms of too high antibiotic concentrations?

A 0-1 patient
B 2-3 patients
C 3-4 patients
D 4 or more patients
Difficult Balance in Antibiotic Dosing Clinicians’ Dilemma

- Retained Non-Renal Clearance in AKI
- Ensure Adequate Concentration at Target Site
- Extracorporeal Drug Clearance
- Increased Antibacterial Resistance
- Increased VD & Decreased Protein Binding

Concern for Antibiotic Toxicity
- Decreased Renal Clearance
- Reducing Drug Costs

Higher Doses

Lower Doses
# Pharmacokinetic Changes in the ICU

<table>
<thead>
<tr>
<th>PK Change</th>
<th>Ability to Reach Pharmacodynamic Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Overload</td>
<td>Reduced Ability</td>
</tr>
<tr>
<td>↓ Serum Albumin / ↓ Protein Binding</td>
<td>Mixed Effects</td>
</tr>
<tr>
<td>Retained Non-renal Clearance</td>
<td>Reduced Ability</td>
</tr>
<tr>
<td>Aggressive CRRT</td>
<td>Reduced Ability</td>
</tr>
<tr>
<td>Augmented Renal Clearance</td>
<td>Reduced Ability</td>
</tr>
</tbody>
</table>
Fluid Overload

• Must increase loading dose for many drugs
• As volume overload is corrected, doses must change again
## Antibiotic volume of distribution in the critically ill

<table>
<thead>
<tr>
<th>Drug</th>
<th>Critically ill</th>
<th>Healthy volunteers</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>0.41 L/kg</td>
<td>0.25 L/kg</td>
<td>Marik 93</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>20 L</td>
<td>10.1 L</td>
<td>Joynt 01</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.32 L/kg</td>
<td>0.21 L/kg</td>
<td>Hanes 00</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>56.9 L</td>
<td>13.6 L</td>
<td>Gomez 99</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.69 L/kg</td>
<td>0.72 L/kg</td>
<td>Del Mar Fernandez 07</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0.38 L/kg</td>
<td>0.08 L/kg</td>
<td>Brink 09</td>
</tr>
</tbody>
</table>
Patient Size Matters

• You should use an antibiotic loading dose
Non-renal clearance rates of selected drugs in patients with normal renal function and ESRD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal Renal FX (ML/min/70 kg)</th>
<th>ESRD</th>
<th>% Decline in CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>65</td>
<td>29</td>
<td>55</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>40</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>217</td>
<td>130</td>
<td>40</td>
</tr>
<tr>
<td>Imipenem</td>
<td>128</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Procainamide</td>
<td>257</td>
<td>102</td>
<td>60</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>40</td>
<td>6</td>
<td>85</td>
</tr>
</tbody>
</table>
Do We Meet Pharmacodynamic Targets in CRRT?

- 53 CRRT patients receiving meropenem, pip-tazo, cefepime or ceftazidime had serum assayed.
- Serum concentrations remained >4X MIC of Pseudomonas spp. for the recommended time
  - 81% patients treated with Meropenem 1000mg Q 12h
  - 71% with Piperacillin/Tazobactam 4.0/0.5 g Q 6h
  - 53% with Ceftazidime 2000 mg Q 12h
  - 0% with Cefepime 2000 mg Q 12h

- Seyler L et al: Recommended b-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care 2011;15:R137
Dosing antibiotics in septic critically ill patients receiving Renal Replacement Therapies…

Mortality rate of critically ill patients receiving renal replacement therapy (RRT) is ~60% (Uchino et al 2005)

In the USA, severe sepsis & septic shock account for ~10% of all mortality
How do you adjust all doses?

• For example:
  • Vasopressors
  • Pain Meds
  • Sedation Meds
  • Paralytics
How should a clinician decide on antibiotic dosing in ICU RRT patients?

- Should I give everyone a “normal renal” dose?
Give “normal” dose to all?

β-lactam antibiotic concentrations during continuous renal replacement therapy

Marjorie Beumier¹, Giuseppe Stefano Casu¹, Maya Hites², Lucie Seyler², Frederic Cotton³, Jean-Louis Vincent¹, Frédérique Jacobs² and Fabio Silvio Taccone¹*

Beumier et al. Critical Care 2014, 18:R105
http://ccforum.com/content/18/3/R105

- 90% patients met or exceeded pharmacodynamic goals
- 53% had dangerously high antibiotic levels
Key Takeaways

• Key Takeaway #1
  • Learn how to read the machine to determine how much effluent (dialysate + ultrafiltrate) is coming out of patient. Effluent = mechanical GFR!

• Key Takeaway #2
  • Use doses on high end of range vs. low end of range for AKI patients receiving CRRT.

• Key Takeaway #3
  • Although the “C” in CRRT is Continuous, sometimes CRRT is interrupted. Be ready to reduce doses if CRRT stops

• Key Takeaway #4
  • Anticoagulation very important. Know which type you use and monitor accordingly
If there are no published RRT antibiotic dosing recommendations...

**DO**

- Consider the effluent rate as the “mechanical GFR”.
- If there is residual renal function as measured by urine output, add that to the effluent rate to figure out an empiric dose.
- Be aggressive early – Loading Dose
- Therapeutic drug monitoring if possible.

**DO NOT**

- DO NOT use MDRD, E-GFR, Cockcroft-Gault, etc to calculate a creatinine clearance on CRRT patients!
- DO NOT use the usual hemodialysis dose – Use more!
My “Best Practices” for Antibiotic Dosing in ICU and RRT

• They can be summed up easily…
Be Aggressive in your CRRT Antibiotic Dosing!
• The main advantage of CRRT over other types of renal replacement therapies is which one of the following?
  A. Faster electrolyte normalization
  B. Superior fluid control
  C. Faster recovery from acute kidney injury
  D. Lower mortality rates
• Which of the following statements is true regarding CRRT modalities?
  A. CRRT should be performed with a peripheral blood access
  B. CVVH uses a dialysate
  C. IV fluids can be only be given after the filter in CVVH or CVVHDF
  D. CVVH, CVVHD, CVVHDF all use the same types of filters
• Which of the following statements is true regarding CRRT modalities?
  A. Faster effluent rates are associated with improved outcomes
  B. Effluent rates should be adjusted based on patient size
  C. CVVHDF is associated with better patient outcomes than CVVHD or CVVH
  D. Drug dosing in CVVH differs from dosing in CVVHD and CVVHDF
Which one of the following statements is true regarding CRRT anticoagulation?

A. Heparin yields longer filter life than citrate
B. Oral citrate (Shohl’s solution) is as effective as parenteral citrate
C. Citrate use is unaffected by liver disease
D. Citrate anticoagulation requires concomitant calcium administration
Drug dosing in CRRT is most affected by which of the following CRRT conditions?

A. Effluent rate
B. Blood flow rate
C. Net fluid loss
D. Hemofilter type