Continuous Renal Replacement Therapy

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Definition of Terms

- **SCUF** - Slow Continuous Ultrafiltration
- **CAVH** - Continuous Arteriovenous Hemofiltration
- **CAVH-D** - Continuous Arteriovenous Hemofiltration with Dialysis
- **CVVH** - Continuous Venovenous Hemofiltration
- **CVVH-D** - Continuous Venovenous Hemofiltration with Dialysis
Indications for Continuous Renal Replacement Therapy

• Remove excess fluid because of fluid overload
• Clinical need to administer fluid to someone who is oliguric
  – Nutrition solution
  – Antibiotics
  – Vasoactive substances
  – Blood products
  – Other parenteral medications
Advantages of Continuous Renal Replacement Therapy

- Hemodynamic stability
  - Avoid hypotension complicating hemodialysis
  - Avoid swings in intravascular volume
- Easy to regulate fluid volume
  - Volume removal is continuous
  - Adjust fluid removal rate on an hourly basis
- Customize replacement solutions
- Lack of need of specialized support staff
Disadvantages of Continuous Renal Replacement Therapy

- Lack of rapid fluid and solute removal
  - GFR equivalent of 5 - 20 ml/min
  - Limited role in overdose setting
- Filter clotting
  - Take down the entire system
Basic Principles

- Blood passes down one side of a highly permeable membrane
- Water and solute pass across the membrane
  - Solutes up to 20,000 daltons
    - Drugs & electrolytes
- Infuse replacement solution with physiologic concentrations of electrolytes
Anatomy of a Hemofilter

Cross Section
hollow fiber membrane

Outside the Fiber
(eflulent)
Inside the Fiber
(blood)
Basic Principles

- Hemofiltration
  - Convection based on a pressure gradient
  - ‘Transmembrane pressure gradient’
    - Difference between plasma oncotic pressure and hydrostatic pressure

- Dialysis
  - Diffusion based on a concentration gradient
CVVH
Continuous Veno-Venous Hemofiltration

Blood In (from patient)

Blood Out (to patient)

LOW PRESS  ←  HIGH PRESS (Convection)

to waste

Repl. Solution
CVVH
Continuous VV Hemofiltration

• Primary therapeutic goal:
  – Convective solute removal
  – Management of intravascular volume
• Blood Flow rate = 10 - 180 ml/min
• UF rate ranges 6 - 50 L/24 h (> 500 ml/h)
• Requires replacement solution to drive convection
• No dialysate
Continuous venovenous hemofiltration
“In vitro” ultrafiltration with blood (post-dilution) (values ± 15%) (Bovine blood at 37° C, Hct 32%, Cp 60g/l)
CVVHDF
Continuous Veno-Venous Hemodiafiltration

Blood In (from patient)

Blood Out (to patient)

Dialysate Solution

Repl. Solution

LOW PRESS ← HIGH PRESS (Convection)
LOW CONC ← HIGH CONC (Diffusion)

to waste
CVVHDF
Continuous VV Hemodiafiltration

- Primary therapeutic goal:
  - Solute removal by diffusion and convection
  - Management of intravascular volume
- Blood Flow rate = 10 - 180 ml/min
- Combines CVVH and CVVHD therapies
- UF rate ranges 12 - 24 L/24h (> 500 ml/h)
- Dialysate Flow rate = 15 - 45 ml/min (~1 - 3 L/h)
- Uses both dialysate (1 L/h) and replacement fluid (500 ml/h)
Pharmacokinetics of Continuous Renal Replacement Therapy
Basic Principles

- Extracorporeal clearance \( (Cl_{EC}) \) is usually considered clinically significant only if its contribution to total body clearance exceeds 25 - 30%

\[
Fr_{EC} = \frac{Cl_{EC}}{Cl_{EC} + Cl_{R} + Cl_{NR}}
\]

- Not relevant for drugs with high non-renal clearance
- Only drug not bound to plasma proteins can be removed by extracorporeal procedures
### Determinants of Drug Removal by CRRT

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Same as hemodialysis but increased MW range</td>
</tr>
<tr>
<td>Membrane</td>
<td>Permeability</td>
</tr>
<tr>
<td>Renal replacement technique</td>
<td>Sieving Coefficient</td>
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<tr>
<td></td>
<td>Convection ± diffusion Cl</td>
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<tr>
<td></td>
<td>Flow rates</td>
</tr>
<tr>
<td></td>
<td>Blood, Dialysate, UF</td>
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<tr>
<td></td>
<td>Duration of CRRT</td>
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</tbody>
</table>
Sieving Coefficient (S)

- The capacity of a drug to pass through the hemofilter membrane

\[ S = \frac{C_{uf}}{C_p} \]

- \( C_{uf} \) = drug concentration in the ultrafiltrate
- \( C_p \) = drug concentration in the plasma

- \( S = 1 \)  Solute freely passes through the filter
- \( S = 0 \)  Solute does not pass through the filter

\[ CL_{HF} = Q_f \times S \]
Determinants of Sieving Coefficient

- Protein binding
  - Only unbound drug passes through the filter
  - Protein binding changes in critical illness
- Drug membrane interactions
  - Not clinically relevant
- Adsorption of proteins and blood products onto filter
  - Related to filter age
  - Decreased efficiency of filter
Relationship Between Free Fraction ($fu$) and Sieving Coefficient ($SC$)
Dialysate Saturation ($S_d$)

- Countercurrent dialysate flow (10 - 30 ml/min) is always less than blood flow (100 - 200 ml/min)
- Allows complete equilibrium between blood serum and dialysate
- Dialysate leaving filter will be 100% saturated with easily diffusible solutes
- Diffusive clearance will equal dialysate flow
Dialysate Saturation ($S_d$)

$$S_d = \frac{C_d}{C_p}$$

- $C_d = \text{drug concentration in the dialysate}$
- $C_p = \text{drug concentration in the plasma}$

- Decreasing dialysate saturation
  - Increasing molecular weight
    - Decreases speed of diffusion
  - Increasing dialysate flow rate
    - Decreases time available for diffusion

$$\text{Cl}_{HD} = Q_d \times S_d$$
CVV HDF Clearance

Continuous venovenous hemofiltration - post dilution

QB = 150 ml/min - QD = 2000 ml/h (in vitro saline)
Extracorporeal Clearance

- **Hemofiltration clearance** ($C_l_{HF} = Q_f \times S$)
  
  $Q_f$ = Ultrafiltration rate
  
  $S$ = Seiving coefficient

- **Hemodialysis clearance** ($C_l_{HD} = Q_d \times S_d$)
  
  $Q_d$ = Dialysate flow rate
  
  $S_d$ = Dialysate saturation

- **Hemodialfiltration clearance**
  
  $$C_l_{HDF} = (Q_f \times S) + (Q_d \times S_d)$$
Case History

- AP 36yo HM s/p BMT for aplastic anemia
- Admitted to ICU for management of acute renal failure
- CVVH-D initiated for management of uremia
- ICU course complicated by pulmonary failure requiring mechanical ventilation, liver failure secondary to GVHD and VOD, and sepsis
Case History
Antibiotic Management on CRRT

- Gentamicin 180 mg IV q24h
- Vancomycin 1 g IV q24h
- Dialysis rate 1000 ml/hour
  - 12 hour post gentamicin levels: 3 - 4 mg/L
  - 12 hour post vancomycin levels: 20 - 23 mg/L
- Dialysis rate increased to 1200 ml/hour
  - 12 hour post gentamicin levels: < 0.4 mg/L
  - 12 hour post vancomycin levels: < 4 mg/L
Dosage Adjustments in CRRT

- Will the drug be removed?
  - Pharmacokinetic parameters
    - Protein binding < 70 - 80%
      - Normal values may not apply to critically ill patients
    - Volume of distribution < 1 L/kg
    - Renal clearance > 35%

- How often do I dose the drug?
  - Hemofiltration: ‘GFR’ 10 - 20 ml/min
  - Hemofiltration with dialysis: ‘GFR’ 20 - 50 ml/min
Drug Removal During CRRT

- Recommendations not listed in PDR
- Limited to case reports or series of patients
- Different filter brands, sizes, flow rates
- Limited information in many reports
  - Rarely report % of dose removed
- Many journals will not publish case reports
- Artificial models and predictions have no clinical value
Dosage Adjustments in CRRT

• **Loading doses**
  - Do not need to be adjusted
  - Loading dose depends solely on volume of distribution

• **Maintenance doses**
  - Standard reference tables
  - Base on measured loses
  - Calculate maintenance dose multiplication factor (MDMF)
Dosage Adjustments in CRRT

- Frequent blood level determinations
  - Aminoglycosides, vancomycin
- Reference tables
  - Bennett's tables or the PDR recommendations require an approximation of patient's GFR
  - The CVVH ‘GFR’ is approximated by the ultrafiltrate rate (UFR), plus any residual renal clearance
  - Using Bennett's or the PDR’s tables, in most CVVH patients, drug dosing can be adjusted for a ‘GFR’ in the range of 10 to 50 ml/min
Supplemental Dose Based on Measured Plasma Level

\[ \text{Dose}_{\text{Suppl}} = \left( C_{\text{target}} - C_{\text{measured}} \right) V_d \]
Adjusted Dose Based on Clearance Estimates

$$\text{MDMF} = \frac{\text{CL}_{EC} + \text{CL}_R + \text{CL}_{NR}}{\text{CL}_R + \text{CL}_{NR}}$$
# Comparison of Drug Removal by Intermittent HD and CRRT

<table>
<thead>
<tr>
<th>DRUG</th>
<th>$CL_R + CL_{NR}$ (mL/min)</th>
<th>$MDMF$ INTERMITTENT HEMODIALYSIS</th>
<th>$MDMF$ CONTINUOUS RENAL REPLACEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>11.2</td>
<td>1.6</td>
<td>2.2</td>
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<tr>
<td>Ceftriazone</td>
<td>7.0</td>
<td>1.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>188</td>
<td>1.0</td>
<td>2.4</td>
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<tr>
<td>Theophylline</td>
<td>57.4</td>
<td>1.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6</td>
<td>3.9</td>
<td>4.9</td>
</tr>
</tbody>
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