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
- SLED – Sustained Low-Efficiency Dialysis

Indications for 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

Advantages of SLED

- Hemodynamic stability
  - Avoid hypotension complicating hemodialysis
  - Avoid swings in intravascular volume
- High solute clearance
- Flexible scheduling
- Lack of need for expensive CRRT machines
- Lack of need for custom 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
    - SLED – Developing role
- 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

- Blood in
- Dialysate in
- Cross Section
- Hollow fiber membrane
- Outside the Fiber (effluent)
- 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)

Repl. Solution

to waste

• 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

CVVH Performance

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

• 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)

SLED
Sustained Low-Efficiency Dialysis

• Primary therapeutic goal:
  – Solute removal by diffusion
  – Management of intravascular volume
• Blood Flow rate = 100-300 ml/min
• Dialysate Flow rate = 100-300 ml/min
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

- Drug: Same as hemodialysis but increased MW range
- Membrane: Permeability, Size, Sieving Coefficient
- Renal replacement technique: Convection ± diffusion Cl, Flow rates, Blood, Dialysate, UF, Duration
**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

  \[ CL_{HF} = Q_i \times S \]

**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<sub>d</sub>)

- 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<sub>d</sub>)

\[ S_d = \frac{C_d}{C_p} \]

- \( C_d \) = drug concentration in the dialysate
- \( C_p \) = drug concentration in the plasma
- Decreasing dialysate saturation
  - Increasing molecular weight
    - Decreases speed of diffusion
  - Increasing dialysate flow rate
    - Decreases time available for diffusion

\[ Cl_{HD} = Q_d \times S_d \]

CVVHDF Clearance

Continuous venovenous hemofiltration - post dilution

Q<sub>B</sub> = 150 ml/min - QD = 2000 ml/h (in vitro saline)
**Extracorporeal Clearance**

- Hemofiltration clearance \( C_{HF} = Q_f \times S \)
  - \( Q_f \) = Ultrafiltration rate
  - \( S \) = Seiving coefficient
- Hemodialysis clearance \( C_{HD} = Q_d \times S_d \)
  - \( Q_d \) = Dialysate flow rate
  - \( S_d \) = Dialysate saturation
- Hemodialfiltration clearance
  \( C_{HDF} = (Q_f \times S) + (Q_d \times S_d) \)

**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/SLED

- 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
  - SLED: ‘GFR’ 10 – 50 ml/min

Dosage Adjustments in CRRT/SLED

- 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 or blood levels
  - Calculate maintenance dose multiplication factor (MDMF)

Supplemental Dose Based on Measured Plasma Level

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

$$MDMF = \frac{CL_{EC} + CL_R + CL_{NR}}{CL_R + CL_{NR}}$$

Comparison of Drug Removal by Intermittent HD and CRRT

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<th>DRUG</th>
<th>$CL_R + CL_{NR}$ (mL/min)</th>
<th>MDMF</th>
<th>INTERMITTENT HD</th>
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Comparison of Drug Removal by SLED and CRRT

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