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

Outside the Fiber
(effluent)

Inside the Fiber
(blood)

Cross Section

hollow fiber membrane

blood in

dialysate out

dialysate in

blood out
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
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
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

Dialysate Solution

Blood In
(from patient)

Blood Out
(to patient)

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)
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 ($\text{Cl}_{\text{EC}}$) is usually considered clinically significant only if its contribution to total body clearance exceeds 25 - 30%.

$$\text{Fr}_{\text{EC}} = \frac{\text{Cl}_{\text{EC}}}{\text{Cl}_{\text{EC}} + \text{Cl}_{\text{R}} + \text{Cl}_{\text{NR}}}$$

• 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

\[ \text{CL}_{HF} = Q_f \times S \]
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 \( (S_d) \)

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

- \( C_d \) = 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

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

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

\[ \text{Dose}_{\text{Suppl}} = \left( C_{\text{target}} - C_{\text{measured}} \right) V_d \]
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>
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<td>INTERMITTENT HEMODIALYSIS</td>
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<td>3.9</td>
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## COMPARISON OF DRUG REMOVAL BY SLED AND CRRT

<table>
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<tr>
<th>DRUG</th>
<th>$CL_R + CL_{NR}$ (mL/min)</th>
<th>SLED</th>
<th>MDMF CONTINUOUS RENAL REPLACEMENT</th>
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