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

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) → REPL. Solution → Blood Out (to patient)
LOW PRESS ↔ HIGH PRESS (Convection) → 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)

LOW PRESS

HIGH PRESS (Convection)

LOW CONC

HIGH CONC (Diffusion)

to waste

No dialysate
**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)

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**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%

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

- 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, Sieving Coefficient
- Renal replacement technique: Convection + diffusion, CI, Flow rates, Blood, Dialysate, UF, Duration of CRRT

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
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

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

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

\[ C_{\text{HD}} = Q_d \times S_d \]
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
  \( S \) = Selving 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 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 losses
  - 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>$\text{CL}_D + \text{CL}_A$ (mL/min)</th>
<th>MDMF INTERMITTENT REMOVALYSIS</th>
<th>MDMF CONTINUOUS RENAL REPLACEMENT</th>
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<tr>
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<td>1.6</td>
<td>2.2</td>
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<tr>
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<td>VANCOMYCIN</td>
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